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GMP Annex 1 and Your Contamination Control

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Focus: Production

2023-2024

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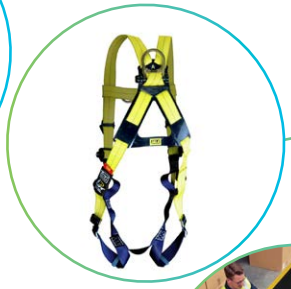

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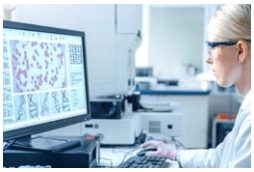

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GMP Annex 1 – How to Validate Protective Cleanroom Garments

By Steve Marnach

After a long consultation period, the revision of the GMP Annex 1 for the manufacturing of sterile products was finally published on the 25th of August, 2022. The lengthy consultation period combined with the document's expansion from 16 to 58 pages indicates that this revision will have repercussions on the technologies and procedures used in pharmaceutical manufacturing, and to the approach that needs to be taken when validating cleanrooms.

The following excerpt from the very first page of the 2nd draft summarises the new approach: "Processes, equipment, facilities and manufacturing activities should be managed in accordance with QRM (Quality Risk Management) principles that provide a proactive means of identifying, scientifically evaluating and controlling potential risks to quality." It will be expected that all the activities inside pharmaceutical manufacturing will be governed holistically by QRM principles and documented in the contamination control strategy (CCS). It will be expected that the CCS is a living document, based on a data-driven scientific approach. It should be continuously updated and improved to control potential risks to quality. The new draft calls for a proactive approach and monitoring, reacting to and correcting detected contamination will no longer be enough. It will be expected from the manufacturers that they fully understand their processes and procedures, so that they identify upfront potential risks to quality, put in place all the technical and procedural means to control these risks, while aiming for continuous improvements. Since cleanroom garment systems are a critical part of sterile and aseptic manufacturing, they obviously need to be managed under QRM principles too. The following is clearly stated in the new GMP Annex 1: "The protective clothing should minimise shedding of fibres or particles and retain particles shed by the body. The particle shedding and the particle retention efficiencies of the garments should be assessed during the garment qualification".

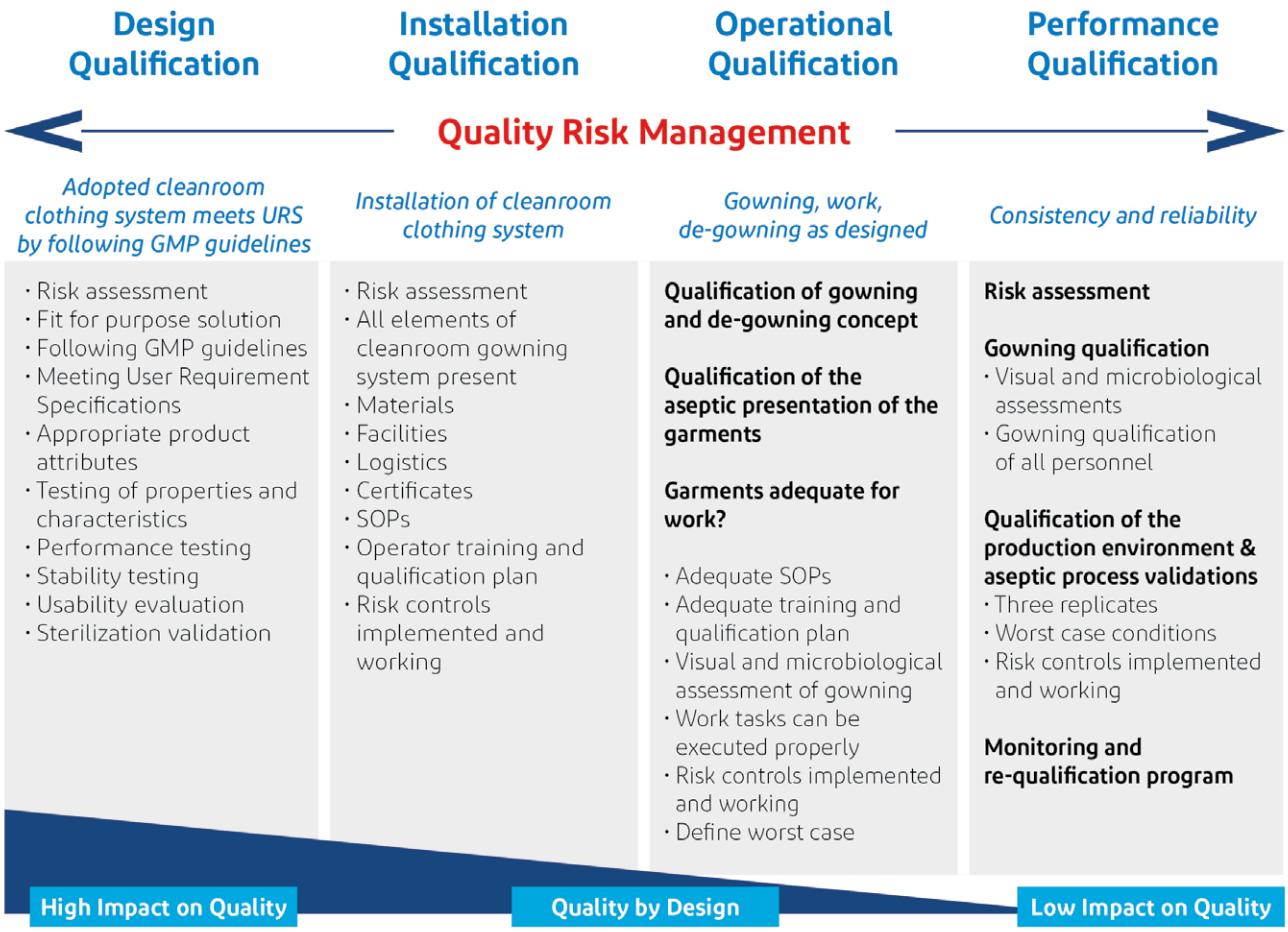
QRM PRINCIPLES FOR CLEANROOM GARMENTS

Cleanroom garment assessment should be run under QRM principles. Quality risk management starts with an analysis and understanding of all the risks to quality linked with cleanroom operators wearing cleanroom garments. A complete data-based analysis will allow the design certification, qualification, validation and monitoring procedures which have quality built into them, thus being part of a holistic contamination control strategy. A risk analysis is needed to understand the contamination risks coming from operators wearing cleanroom garments. It has been scientifically demonstrated for many years that operators represent the biggest source of contamination inside the cleanrooms and represent 75% of all contaminants[1]. This contamination comes both from the operators themselves and from their cleanroom garments. Human contamination coming from operators is due both to human nature (an average person sheds 40 000 particles per minute and 10% of them carry microorganisms) and human behaviour[2]. While it is possible to mitigate the latter aspect through careful operator selection, training, slow movements or impeccable hygiene, the fact is operators will always shed particles, as multiple studies have proven. The only measure to prevent those particles generated by operators from contaminating the cleanroom are the cleanroom garments, they are the only barrier between the operator and the production environment. The 2020 draft of Annex 1 clearly points this out: "(the cleanroom garments should) retain particulates shed by the body".

The cleanroom garments themselves may be a source of contamination should not be neglected and this risk needs to be assessed too. For example, the material used for making the garments (non-woven for single-use garments, or woven for the reusables) can shed more or fewer particles depending on the nature of the fibres or filaments used, their resistance to abrasion or their construction, as well as the effect of multiple wash-dry-sterilisation cycles. The trims (zip, buttons, elastics or sewing threads) too, may be a source of contamination. The design of the garment plays a role too and should be evaluated. One detail which is often neglected is the packaging in which the cleanroom garments come. This could be a source of contamination too (i.e., paper-back bag vs. plastic bags).

MAIN STAGES OF THE VALIDATION

Once the risks have been evaluated, they should be, as far as possible, removed or replaced by technical or organisational means and the residual risks mitigated as much as possible using a validated cleanroom garment system. In their article "Risk & Science-Based Validation of Cleanroom Garments" from 2019, M. Pavičić and T. Wagner have offered a QRM-based structured approach to validate cleanroom garments that meets EU general guidance on validation (GMP Annex 1519)[3].



MATERIAL QUALIFICATION	PERFORMANCE TESTING	STABILITY TESTING	USABILITY EVALUATION
Cleanroom garments	*Cleanroom garments*	*Single-Use garments*	*User scenarios*
· Fiber and particle shedding · Sterilization compatibility · Sterility assurance level · Particle filtration efficiency · Bacterial filtration efficiency · Porosity · Surface resistivity · Perforation resistance · Mechanical resistance · Protection against biological agents	· Body box testing · Helmke drum test	· Properties and characteristics at the end of shelf life *Reusable garments* · Properties and characteristics after maximum number of laundering and sterilization cycles	· Transfer to classified storage area · Readability of label · Easy opening of packaging · Aseptic unfolding of garments · Gowning · Donning additional accessories (e.g., sterile gloves, face mask, goggles) · Work situations · Safety, biosafety · De-gowning
Packaging	*Sterile packaging*	*Sterile packaging*	*Packaging*
· Fiber and particle shedding · Bioburden · Penetration of commonly used disinfectants *Sterile packaging* · ISO 11607-1	· Influence of transport on integrity/sterility (ISO 11607-1)	· Packaging integrity/ sterility at the end of shelf life (ISO 11607-1)	· Aseptic presentation of garments (multiple layers)

Source: Pavičić M. & Wagner T., "Risk & Science-Based Validation of Cleanroom Garments", IVT Network 2019

GMP Annex 1 calls for scientific evaluation and control of all potential risks to quality. It is, therefore, logical that the evaluation of cleanroom garments must also be based on scientific test data that allows for the performance of garments as well as enabling control of these performances over the lifetime of the garment. Simply relying on experience, visual checks and recommendations from the suppliers will no longer be enough for authorities. In their paper, M. Pavičić and T. Wagner have suggested a series of criteria for validating cleanroom garments that can be measured, scientifically tested and documented, thus meeting the expectations of the new GMP Annex 1 (see table above).

In this article, some of these test methods will be explained with their advantages, as well as their disadvantages.

MATERIAL QUALIFICATION TESTS

As stated above, the most important function of cleanroom garments is to make sure they retain a maximum amount of particles shed by the operator. As human beings constantly shed particles and microorganisms, we must rely on cleanroom garments to make sure that they stay inside the cleanroom garment and do not risk contaminating the cleanroom. It is, therefore, important to assess the filtration efficiencies of the garments. This is determined both by the structure of the material out of which the garments are made, and the construction of the garments themselves (i.e., seams and design). The former will be addressed in this paragraph and the latter in the section on garment qualification.

1) Particle filtration efficiency (PFE) measures the filtration efficiency of the material used for cleanroom garments against dry particles shed by the operators (e.g., skin flakes, even when stationary, people generate approximately 100 000 particles of 0,3 µm or greater). The dry particle filtration of materials depends on the pore size of the fabric, the smaller the pore size, the higher the filtration efficiency. It may be assessed with the test method EN 143 (TSI 8130), which measures the filtration efficiency using salt particles having a diameter of 0,3 µm. Since this is the smallest size of particles shed by humans, and since the smallest size of particles used for pharmaceutical cleanroom

classification is 0,5 micron, this test is appropriate for assessing the PFE of the materials, but since it assesses the fabrics only, it cannot be used alone.

2) Bacterial filtration efficiency (BFE) measures the filtration efficiency of the material used for cleanroom garments against bacteria shed by operators. Humans release microorganisms through skin flakes (microbe-carrying particles) or sweat. Microbe-carrying particle filtration efficiency is again determined by the pore size and may be assessed by the EN 143 test as well or by ISO 22612 which measures the resistance to penetration by biologically contaminated solid particles. Liquid filtration efficiency is determined by the absorbency of the fabric, the more liquid repellent a fabric is, the higher its filtration efficiency. The ASTM F2101 standardised test method evaluates bacterial filtration efficiency using a biological aerosol (Staphylococcus aureus) with a droplet size of 3 micron. While this test was originally developed for medical face masks, it can also be used for assessing other materials, and is relevant for cleanroom garments as well since Staphylococci represent one of the highest sources of human contamination inside the cleanroom. While yielding pertinent results, this is also a material test only and, therefore, should not be used as a sole assessment point.

TESTS FOR GARMENT QUALIFICATION

Particle retention performance is not only determined by the materials used, but also by the construction and the design of the cleanroom garments themselves. The IEST (Institute of Environmental Sciences and Technology) has developed test recommendations and methods for assessing the particle - shedding and particle-retention performances of cleanroom garments which would be very useful for the qualification of cleanroom garment systems.

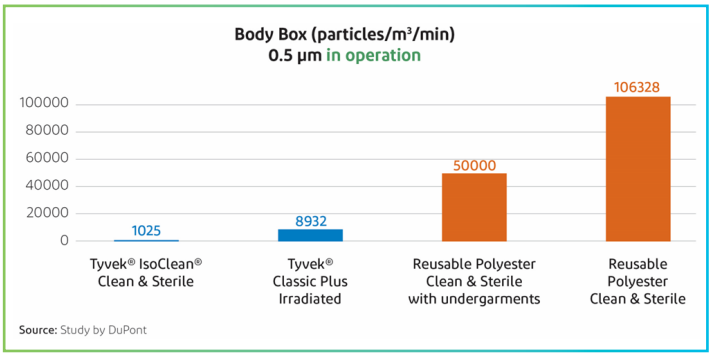
1) The Helmke Drum test method as per IEST-RP – C003.4: it is a rotating drum, with a rotating speed of 10 turns per minute, in which the cleanroom garments are being tumbled while a particle counter inside the drum measures the concentration of particles per minute for sizes 0,3 micron and 0,5 micron. The results are then classified into three categories based on the number per size of particles released.

Helmke Drum test result classification for coveralls

Category	Particle concentration	
	Particles ≤ 0,3 µm/minute	Particles ≤ 0,5 µm/minute
I	< 2000	< 1200
II	2000 - 20 000	1200 - 12 000
III	20 000 - 200 000	12 000 - 120 000

This non destructive test method only measures the particle release of cleanroom garments and is, therefore, quite widely used by cleanroom laundries to control the efficiency of their washing processes, but it has also been used by scientific studies to assess particle release over time for cleanroom garments that are washed multiple times[4]. Since these studies have demonstrated that particle release increases with each wash-dry-sterilisation cycle, the Helmke Drum test method may also be used for assessing particle shedding over time to define the moment when cleanroom garments need to be replaced. A visual inspection of the garments after washing is not enough to detect degradation of the particle release of the cleanroom garments. However, the Helmke Drum test method is not able to assess particle filtration efficiency of cleanroom garments, so should not be used as a unique qualification criteria.

2) The Body Box test (IEST-RP-CC003.4) is done inside a small cleanroom cabin in which an operator (wearing a cleanroom garment system) performs a series of pre-defined movements during which the particles inside the body box are measured and counted. For the time being, this is the test closest to real wear conditions inside cleanrooms. It measures both the particle release of the cleanroom garments while they are being worn and the particle filtration efficiency of the garments. The less particles garments shed and the better the particle filtration efficiency of the garments is, the lower the measured particles will be. Here are some examples:



Since this is a non-destructive test, it may also be used for assessing the performance of cleanroom garments which are washed multiple times in order to assess the moment when they need to be replaced. Various studies, such as those of Ljungqvist B. and Reinmüller B[5]., show here also that the performance of reusable cleanroom garments goes down over time. As close to real work conditions as the body box may be, it does have the

drawback that the test also measures the particle release of the test person without being able to distinguish which particles stem from the operator and which are released by the garment itself. As the study from Whyte et al[6] shows, humans have a highly variable rate of particle shedding. Therefore, comparative tests are only meaningful if the same test person is used for running body box tests of different cleanroom garment systems or cleanroom garments that are more or less old. Under the right test procedures, the body box is an excellent test for validating cleanroom garment systems.

ASSESSMENT OF CLEANROOM GARMENT STERILITY

In aseptic manufacturing (grades A/B) only sterile cleanroom garment systems may be used. It is expected that the sterilisation process is based on data, fully documented and is part of a contamination control strategy. Following a radiation sterilisation process which can guarantee a sterility assurance level of 10^{-6} as per ANSI/AAMI/ISO 11137-1, is recommended to make sure the sterilisation process is validated and controlled. The steriliser, manufacturer or laundry of cleanroom garments should be able to provide a certificate of sterility. A simple certificate of irradiation or a protocol stating the temperature and duration of the autoclaving process will not be sufficient anymore.

CONCLUSION

Since operators represent the highest contamination risk inside cleanrooms, cleanroom garment systems are a critical part of a contamination control strategy. The new GMP Annex 1 asks for a proactive, holistic, risk-based, and data-driven process validation. It will become necessary that the selection of the cleanroom garment system is based on scientific data and not only on experience, wearers' comfort and/or costs. Using recognised testing methods (like those suggested in this paper) to assess the performances of cleanroom garment systems and to determine their end of life, should be part of a structured and well documented approach which would fit well into a QRM-based contamination control strategy, and thus meet the expectations of the latest regulatory requirements.

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Annex 1 and the Impact on Cleanroom Wipe Selection

In August, 2022 the final version of the new Annex 1, part of the EU-GMP guidelines for aseptic manufacturing was published

By Meike Wix, Texwipe

A revision was urgently required to adapt the existing guidelines to new technologies and methods. This new version comprises a total of 58 pages with 11 chapters for a considerably extended scope of application. The following sentence is particularly interesting "…. includes additional areas (other than sterile products) where the general principles of the annex can be applied".

The importance of Quality Risk Management (QRM) is now even more clearly emphasised and seen as the basis for justifying possible deviations - supported by a corresponding risk assessment.

This then leads us directly to the requirement to implement a Contamination Control Strategy (CCS) as a comprehensive concept for contamination control across an entire manufacturing area.

Central aspects of this documented Contamination Control Strategy include inter alia the system design, premises and equipment, personnel, also cleaning and disinfection and monitoring systems - to name just a few.

But how can cleanroom wipers be classified here? They are not explicitly mentioned in the new Annex 1, but are of course part of every cleaning procedure and, therefore, subject to a corresponding risk analysis and assessment.

It should be noted that the primary goal of cleaning is to remove contamination without introducing new contaminants through this process or the materials used for it. In order to be able to carry out a proper risk assessment here, it is first necessary to precisely determine the individual requirements:

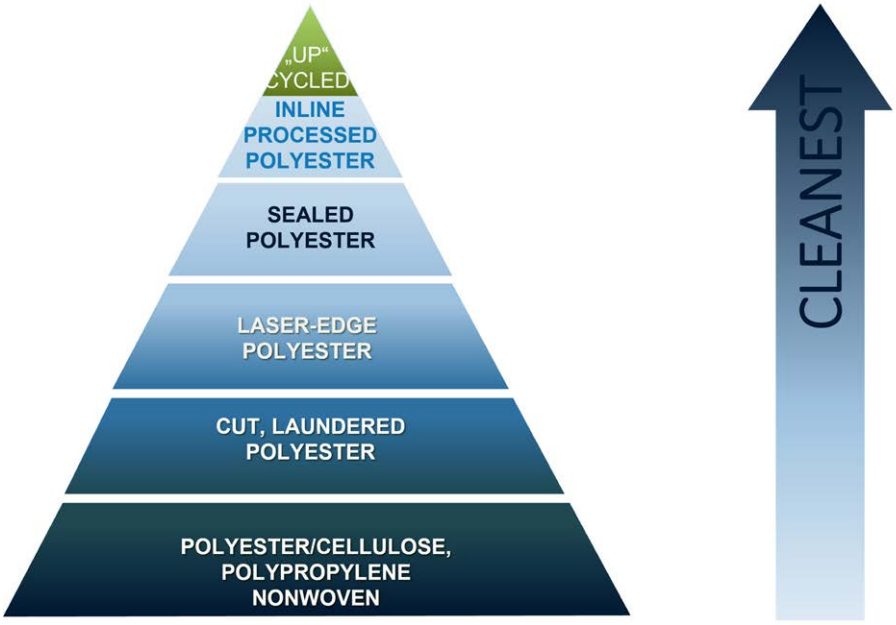
- What are the contaminants to be removed? Particles, microorganisms, endotoxins, ions...?
- In which working environments should the wipers be used?
- ISO class, GMP class, isolator, RABS?
- Which chemicals are used with the wipers?
- Detergents, disinfectants?
- Are there any additional requirements?
  - Packaging (e.g., VHP Barrier Bag)
  - Packaging size
  - Wiper size
  - Wiper count/packaging unit
- Are there quality certificates available or other documentation?
- Are audits necessary/possible?

Once all these have been defined, the next step is to select a wiper that meets these requirements.
Is it sufficient for this and for the subsequent risk analysis to select and compare wipes based on a data sheet?

We at Texwipe say: NO - that's definitely not enough! At best, it can provide a first orientation, but more is needed for a proper risk assessment.

For example, what do you know about cleanroom wipers and the effect of material, type of fabric and manufacturing process on the level of cleanliness and quality? Let's take a look at this.

Let's start with the material or substrate. In general, it can be said that plastic substrates are 'cleaner' (i.e. generate fewer particles) than natural ones such as cellulose or cotton. But there are also major differences within the plastic and plastic families.



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The next point is the type of fabric – how the substrates are processed. The pyramid shows that knitted polyester proves to be 'cleaner' than e.g., fleece fabric (non woven). In addition to this, the effect that possible edge sealing plays as a major role in minimising particle release.

But the manufacturing process also plays a role that should not be neglected, and you will usually not learn anything about this in the available data sheets.

Texwipe is the only manufacturer worldwide to develop and use the three manufacturing processes with different levels of automation described below.

Although all processes take place in certified cleanrooms, increasing automation naturally goes hand in hand with a reduction in biological contamination caused by humans.

Nevertheless, most cleanroom wipers produced worldwide are still manufactured conventionally in a very manual process, in which the wipers are washed and dried in conventional industrial machines after cutting, and the downstream manufacturing steps (e.g. stacking and packaging) are done by employees more or less manually.

- Conventional laundry
- Manually focused process

- Semi automated
- Partially manual process

- Fully automated
- Virtually no manual processes

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As early as the 1990s, Texwipe developed the Vectra-Process a semi-automated manufacturing process. As a result, the washing and drying procedure was automated and changed in such a way that the particle generation from wipers produced could be reduced even more. Due to fewer employees in the cleanroom and especially in the area in front of the packaging area, there was less biological contamination expected here.

But as in all areas of pharmaceutical production and related industries, the focus at Texwipe is on further automation, and the first fully automated wipe production was developed with the Vertex process. From washing up to final packaging in sealed bags, the wipers are manufactured in a micro-cleanroom located in a certified cleanroom without human intervention. This globally unique manufacturing process allows Texwipe to consistently offer low particle and bioburden-reduced wiper in our standard portfolio.

But sometimes even that is not enough for very special requirements. It may then be necessary to develop customer-specific products that contribute to contamination control and, therefore, to risk minimisation even better than any standard wiper.

It is certainly a great advantage that Texwipe was able to set up a local production site in the EU (Netherlands), which makes it possible to develop such customer-specific products in close cooperation with European drug manufacturers. And, of course, all sterile products, whether from the standard portfolio or customer-specific, are validated, documented and tested for endotoxins.

Like all Texwipe operations, the one in the Netherlands is ISO 9001:2015 certified and works according to a Global Quality System. Similar to the GMP guidelines, this includes an effective Quality Risk Management and a Contamination Control Strategy. Of course, on a different level than in the aseptic manufacturing of medicinal products, but in principle they are quite comparable.

In summary, one can say that the risk assessment of a cleanroom wiper required according to EU-GMP is only possible if you define your own requirements precisely, and then, with knowledge of materials, manufacturing processes and quality criteria, look for the most suitable product either from the standard portfolio or, if there is nothing suitable there a customer-specific wiper that is developed in a joint project.

Ansell

MAKE SURE YOU'RE DRESSED FOR THE PART

Ansell can provide full head to toe sterile PPE and product protection solutions to ensure you're Annex 1 ready

PART 7.11 LOW LINTING DISPOSABLE GARMENTS

strategically folded to aid aseptic donning.

PART 7.13 GOGGLES & FACEMASK

to ensure full face coverage to prevent the shedding of droplets and particles into the environment.

PART 7.16 & 7.13 GLOVES

Our sterile 300mm/12" gloves are available in Latex (NRL), Neoprene, Nitrile and PI and can be disinfected using alcohol disinfectants** and double-donned to comply with aseptic gowning and SOPs.

PART 7.16 & 7.13 GLOVES

Our longer length 400mm/16" & 600mm/24" gloves provide extra coverage of the arm to make sure no risk of gaps between garment and gloves.

PART 7.11 PACKAGING

All sterile PPE is double or triple bagged in durable, recyclable* plastic packaging to reduce contamination and includes sterilisation indicators to show the PPE has been sterilised to a Sterility Assurance Level (SAL) 10^{-6}.

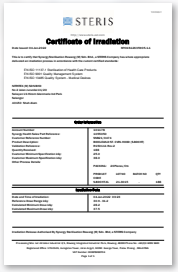
Personnel in a cleanroom are the biggest contamination risk during aseptic processing and Annex 1 Part 7 outlines the requirements needed regarding personnel numbers, behaviour, skills and clothing. The implementation of a precise contamination control strategy is key to ensuring that the PPE they're wearing is suitably assessed and monitored.

All Ansell sterile PPE - gloves, clothing, goggles, RABS/Isolator gloves - has certification to prove they have been subjected to the full sterilisation process and each product within the range comes with a full validation pack including product and quality statements and applicable comprehensive test results.

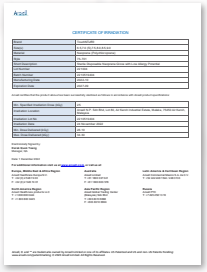
*Always check your local recyclable status of packaging materials in your country.
**Please check product validation pack for full test results.

PART 4.18 - 4.22 BARRIER TECHNOLOGIES

Our sterile Nitrile RABS & Isolator glove range comprises of gloves, mittens and sleeve/glove systems and are 100% water leak tested for glove integrity and resistant to VHP, IPA and disinfectants for in situ sanitizing.


STERIS

Certificate of Irradiation


Ansell

CERTIFICATE OF PENETRATION

PART 7.11 CERTIFICATION

Certificates of Irradiation (Gamma) or Certificates of Processing (EtO) per product lot no. can be downloaded via our easy to use certificate tool on www.ansell.com/life-sciences/certificates.

Annex 1 places considerable emphasis on barrier technology to separate the operator from the product to maintain Grade A conditions. This can be accomplished by the use of RABS or isolators, our range of RABS and Isolator gloves are available in different port sizes and a choice of materials including Nitrile, CSM, NRL, Neoprene, EPDM and EPDM+ the most suitable material will be dependent on the application and can be decontaminated by autoclaving, VHP or IPA**.

Discover all our sterile protection solutions for your aseptic processing needs at **www.vwr.com/ansell**
Or contact your local VWR representative today for more information.

Disinfectant Residues: Mitigation and Management

Problems with residues

Cleanroom residues can be generated processes, raw materials and certainly by people, but a significant contributor to residues in a cleanroom are the disinfectants themselves. Many common and well used disinfectants leave significant residues on a surface, which can subsequently have a detrimental effect on the effectiveness of the disinfectant used. This is acknowledged in the new GMP Annex 1, "For disinfection to be effective, prior cleaning to remove surface contamination should be performed. Cleaning programmes should effectively remove disinfectant residues."

Cleaning and disinfection are two words that have often been used interchangeably, when in fact, they have two different meanings. Annex 1 now clearly states the difference: A process for removing contamination e.g. product residues or disinfectant residues. Cleaning is physically removing non-viable matter from a surface. Disinfection: The process by which the reduction of the number of microorganisms is achieved by the irreversible action of a product on their structure or metabolism, to a level deemed to be appropriate for a defined purpose. The reduction in the amount of viable contamination on a surface. Residue removal is specific to cleaning.

There are currently no approved or validated methods for assessing the amount of residue on a non-product contact surfaces. Many, or even most facilities, will conduct a visual test for residues on non-product contact surfaces only. As previously mentioned, many of the commonly used disinfectants in cleanrooms can themselves leave significant residues on a surface.

Disinfectant residues can cause visual, safety, and product integrity threats, including sticky or slippery floors and doors, streaks and discoloration, and contamination. If residues are not managed correctly, they can also cause degradation to the facility over time, which can lead to costly reconstruction or require deep cleaning measures.

Application of disinfectants and proper use of tools such as wipes and mops play a critical role in residue management, and there are many variables that can pose issues when cleaning and disinfecting including over-application of disinfectants, frequency of residue removal, reapplication of disinfectant (if longer contact times are required), and the nature of the disinfectant. There is no 'one size fits all' approach for mitigation of residues as part of an overall Contamination Control Strategy (CCS).

An initial thought maybe to use a low, or no residue disinfectant to solve this particular issue. There is currently no definition or standard of what constitutes a 'no' or 'low residue' disinfectant. However, there are claims made on disinfectant advertising that a disinfectant is either 'no' residue or 'low' residue. The data to support this is usually a simple residue on evaporation test.

The European Pharmacopoeia has a 'residue on evaporation' test (RoE) which can easily and cheaply be used to quantify the amount of non volatile residue left by a solution. The test method simply requires 100 ml of the solution to be boiled to dryness in an evaporating basin of known weight.

EP RESIDUE ON EVAPORATION METHOD

- Evaporate 100 ml of test substance to dryness in a water bath and dry at 100 to 105 °C for 1 hour.
- Weigh container after drying and subtract weight of the original container.

Two chemicals used as disinfectants which do have an EP monograph are isopropyl alcohol and ethanol, these have limits for residue on evaporation. The limit for 99% isopropyl alcohol is 20 ppm and 25 ppm for 96% ethanol. Both of these products would be universally accepted as leaving no residue on a cleanroom surface. So, a product which leaves a non-volatile residue of less than 25 ppm could be classed as no residue?

The only other commonly used cleanroom disinfectant which leaves a residue as low as alcohol is hydrogen peroxide. Hydrogen peroxide (H_2O_2) breaks down to water and oxygen on a surface, the reaction taking place is $2H_2O_2 \rightarrow 2H_2O+O_2$. Test work carried out on Contec's hydrogen peroxide confirms this with RoE results between 4 and 7 ppm. However, this cannot be assumed for all hydrogen peroxide solutions. It is a solution in equilibrium so different grades of hydrogen peroxide contain different amounts of stabilisers which can contribute to the amount of residue left behind. Blended disinfectants, which contain alcohol or hydrogen peroxide with other chemicals, can also leave considerable residues. Table 1 shows the residue on evaporation levels for a range of cleanroom disinfectants manufactured in both the USA and Europe.

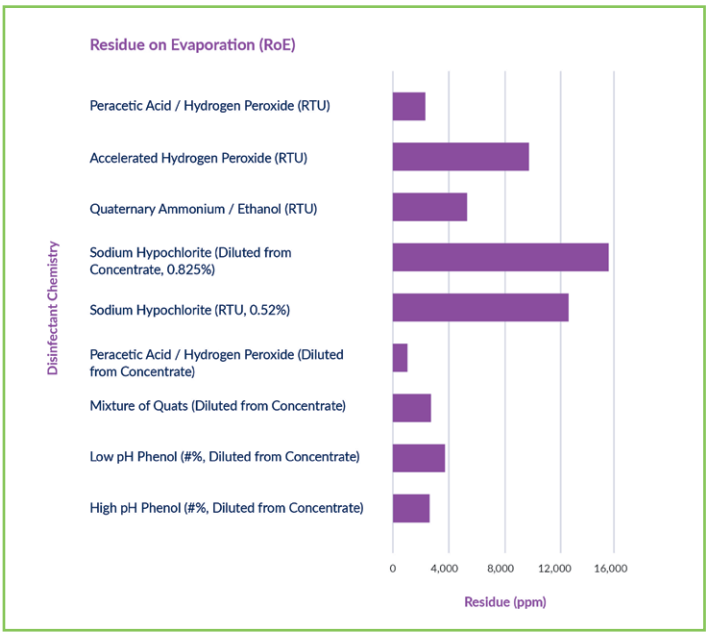


Table 1

As can be seen from the results, the level of residue for the different active ingredients can vary significantly from product to product. The table also shows there can be a difference for disinfectants containing the same active ingredient, which would be due to the concentration of the active ingredient in the product, the amount of stabilisers required, and potentially the addition of preservatives, pH adjusters or odour mitigators.

So, we could just use 70% alcohol and hydrogen peroxide? There are drawbacks to both of these disinfectants, which means other disinfectants may have to be considered. 70% alcohol is highly flammable so it cannot be used over large surface areas, and is also not sporicidal. Hydrogen peroxide is an aqueous-based solution which is non-flammable, but at a safe to use concentration of 6% only, has a low level of sporicidal activity in 60 minutes.

CLEANROOM DISINFECTANT RESIDUE ON A SURFACE

Disinfectant residues can take many forms - clear, white, yellow, pink, solid, gelatinous, crystalline, powdery or sticky. Work carried out by Contec (ReinRaum Technick Mar 2021) showed that the visual appearance of the disinfectant on a surface may not always match the amount of residue shown on a residue on evaporation test. The method of application of the disinfectant will also affect the residue.

The appearance of disinfectant residue on different surfaces within the cleanroom can look lesser or greater for the same amount of residue dependent on the characteristics of the surface itself. Highly polished or reflective surfaces will show residues more easily. It is common to see disinfectant residues on windows, which can make a facility look dirty and unkept. Highly reflective surfaces, such as glass and polished metals, will show the residue more significantly, although the amount of residue will be the same.

IS THERE A BETTER WAY THAN VISUALLY CLEAN?

The current accepted validation for a non-product contact surface being clean, is a visual inspection. Within ASTM-E3263 "Standard Practice for Qualification of Visual Inspection of Pharmaceutical Manufacturing Equipment and Medical Devices for Residues" there are suggestions to make the comparison between operators of 'visually clean' as repeatable and robust as possible. We wanted to find out if we could find a correlation between visibly clean and a quantifiable metric, and if we could make that quantitative method of assessing

residues easy to use and robust for normal use. We carried out work using various methods to quantify residues and residue removal, a gradation scale for visual assessment, using a haze meter on mirrors – a sort of Finite Element Analysis and finally a fluorescent tracer and image pixel analysis.

Using visual analysis and a graduation scale had some benefits as even slight residues were easily discernible. We were still left with the residue being difficult to quantify as it was very subjective and operator dependent. An attempt to measure surface cleanliness using a Haze meter on residues on mirrors was also very objective and time-consuming. The residue was easy to quantify but it was objective. Though overall results could be useful, random and trace residues that were easily visible were not captured and reflected in data. It highlighted the sensitivity of the naked eye to even minute levels of residue.

The residue field was variable and the results inconsistent with visible trace residues. The best results were obtained with the fluorescent tracer and image pixel analysis.

A fluorescent tracer dye was added to 'average residue' disinfectant and applied by wiping. Each application was allowed to dry before an additional layer of disinfectant and, therefore, residue was applied. A camera pixel analysis was used to measure the surface residue. This was easy to quantify, and the full residue field could be analysed with the image pixel analysis. The results obtained were consistent with the visible trace residues. It could be easily conducted on a wide variety of surfaces. The initial test work was carried out on 150x150 mm stainless steel plates with 3x50 mm diameter image analysis areas. We found that the disinfectant residues applied are very irregular and non uniform (splotchy!) probably due to the surface tension interaction with the coupon surface. Because of this, the image analysis area was not always sufficient to give results with accurately correlated which what was visually observed on the coupons.

Additional work was carried out on coupons which were 150x610 mm with 18x50 mm diameter image analysis areas. The much larger image analysis area gave results that more accurately correlated with what was visually observed on the coupons. Understanding that disinfectant residues are very irregular and non uniform due to surface tension interaction with the surfaces, explains why the quantification of the distribution and the total disinfectant residue can be very difficult.

NOT ALL RESIDUES BEHAVE THE SAME

As Table 1 shows, many common disinfectants leave a residue to greater or lesser degrees. Annex 1 states that the cleaning process should be validated so that it can be demonstrated that it can remove any residue that could create a barrier between the decontamination agent and the equipment surface. But not all residues behave in the same way, so consideration should be given, not just to the amount of residue left, but how easily the disinfectant residue is to remove from the cleanroom surfaces. Old and scratched surfaces may also influence residue removal. Some residues are free-rinsing and easy to remove, others are 'sticky' and 'waxy' and can be difficult to remove from a surface. This can also change over time, a residue easily removed immediately after the contact time might not be so easily removed weeks later. If an immediate rinse stage is not to be used, work would need to be carried out to show how long a residue can be left before removal becomes more difficult.

VALIDATION FACTORS

This starts to give an insight into how much validation work may be required to meet the requirements of the new Annex 1 if a 'no residue' disinfectant is not being used. A lab-based 'residue on evaporation' test will give a quantitative result of how much residue a disinfectant will leave, and if it is above 25 ppm per 100 ml, further validation work would be required.

The method of application of the disinfectant will need to be taken into account, as this affects the amount of residue left on a surface in use. The work needs to be carried out on the different surfaces in the cleanroom as the appearance of the residue on the different surfaces varies dependent on the smoothness and reflectiveness of the surface.

If an immediate 'wipe to dry' or rinse stage is not used at the end of contact time, the amount of time the residue can be left before removal needs validating as a residue that can be removed after a week may not be able to be removed after a month. The roughness of a surface will also influence how easily a residue can be removed. The choice of cleaning solution will need to be validated, whether WFI, alcohol or a detergent (surfactant) solution works best. This might not be the same for all disinfectants that you are using.

CONTROLLING DISINFECTANT RESIDUES

One of the simplest ways to control disinfectant residue is to not let it build up in the first place. This can be achieved by changing the cleaning and disinfection SOPs so that a 'wipe to dry' phase is included. Immediately after the validated contact time for the disinfectant, wipe the surfaces to dry with either a dry wipe or mop head.

Alternatively, a disinfectant residue removal step is necessary to mitigate the residue and maintain cleanliness of the surfaces within the cleanroom. It could include the use of 70% alcohol solution or pre-saturated wipes, water for injection or purified water, or 6% hydrogen peroxide. This could be a weekly or bi-weekly removal of disinfectant residues, either immediately after the validated contact time, or prior to the next disinfection application. If using alcohol for residue removal, the health and safety issue of alcohol use over large areas would need to be considered.

If residues are allowed to build up, a regime for a detergent / solvent clean on a monthly or quarterly basis could be considered. If the point at which a residue ceases to become free-rinsing is known, then this would govern the point at which the detergent clean became necessary. As all detergents leave residues this would be a 3-stage process of clean, remove detergent residue and wipe to dry. So, this may not be the least time-consuming option it appears to be. The cleaning agent might need to be more aggressive or corrosive than if the residues are removed more frequently. Whichever decision is taken, it will need to be captured in a 'Contamination Control Strategy' based on risk management and monitored through environmental monitoring.

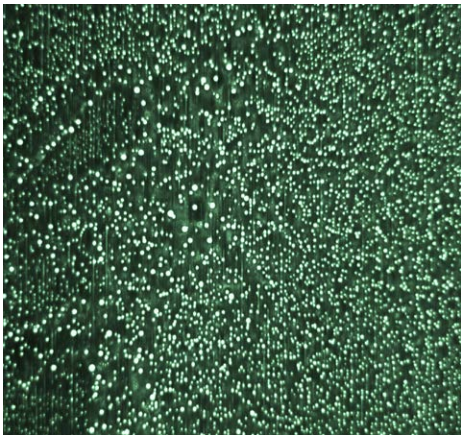
EVALUATION OF RESIDUE REMOVAL PROTOCOLS

We used the fluorescent tracer and image pixel analysis to see if we could see a difference in the residue removal protocols. Eighteen sampling locations were used per replicate and five replicates per trial. A fluorescent tracer dye was added to average residue disinfectant and applied by wiping. Each application was allowed to dry before an additional layer of disinfectant and, therefore, residue was applied. The following procedures were compared.

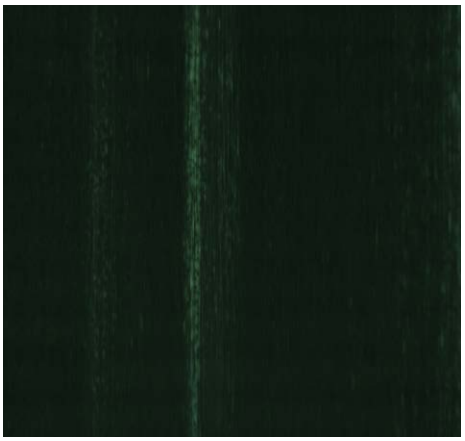
1 - Dry residue, wiped with a dry wipe
2 - Dry residue, wiped with a 70% IPA pre-saturated wipe
3 - Dry residue, sprayed with 70% IPA solution, then wiped with a dry wipe
4 - Dry residue, wiped with a moist wipe
5 - Six layers of dry residue, wiped with a 70% IPA pre-saturated wipe

Pixel analysis was carried out on the clean coupon, after the residue was applied to the coupon and after the coupon had been wiped/sprayed etc. The final calculation was a comparison of average percent residue removed.

Clean surface



Applied residue



Wiped surface (70/30 IPA/DIW)

It will not necessarily come as any surprise, but it can be seen in Table 2 there was a significant difference in the ability to remove a dry residue with a dry wipe versus a pre-saturated wipe. Solubilising the residue also allowed more of the residue to be removed with a pre-saturated wipe than a pre-saturated wipe used on the dry residue. The most effective result was gained by solubilising the residue and using a dry wipe. A similar result could probably be obtained by removing a still wet disinfectant solution with a dry wipe after the contact time. Again, confirmation of what we expected to see was that residue accumulation greatly increases the difficulty in removing the residue from a surface. Further work could be carried out to see if these results are consistent for all disinfectant residues.

CONCLUSION

Disinfectant residues can pose significant cleanliness and operational risks in cleanrooms and other controlled environments, in additional to degrading the appearance of the cleanroom and suggesting a lack of control. Regulatory organisations worldwide recognise the need to remove or otherwise mitigate disinfectant residues as part of an effective overall Contamination Control Strategy. The recently published Annex 1 specifically states that "Cleaning programmes should effectively remove disinfectant residues."

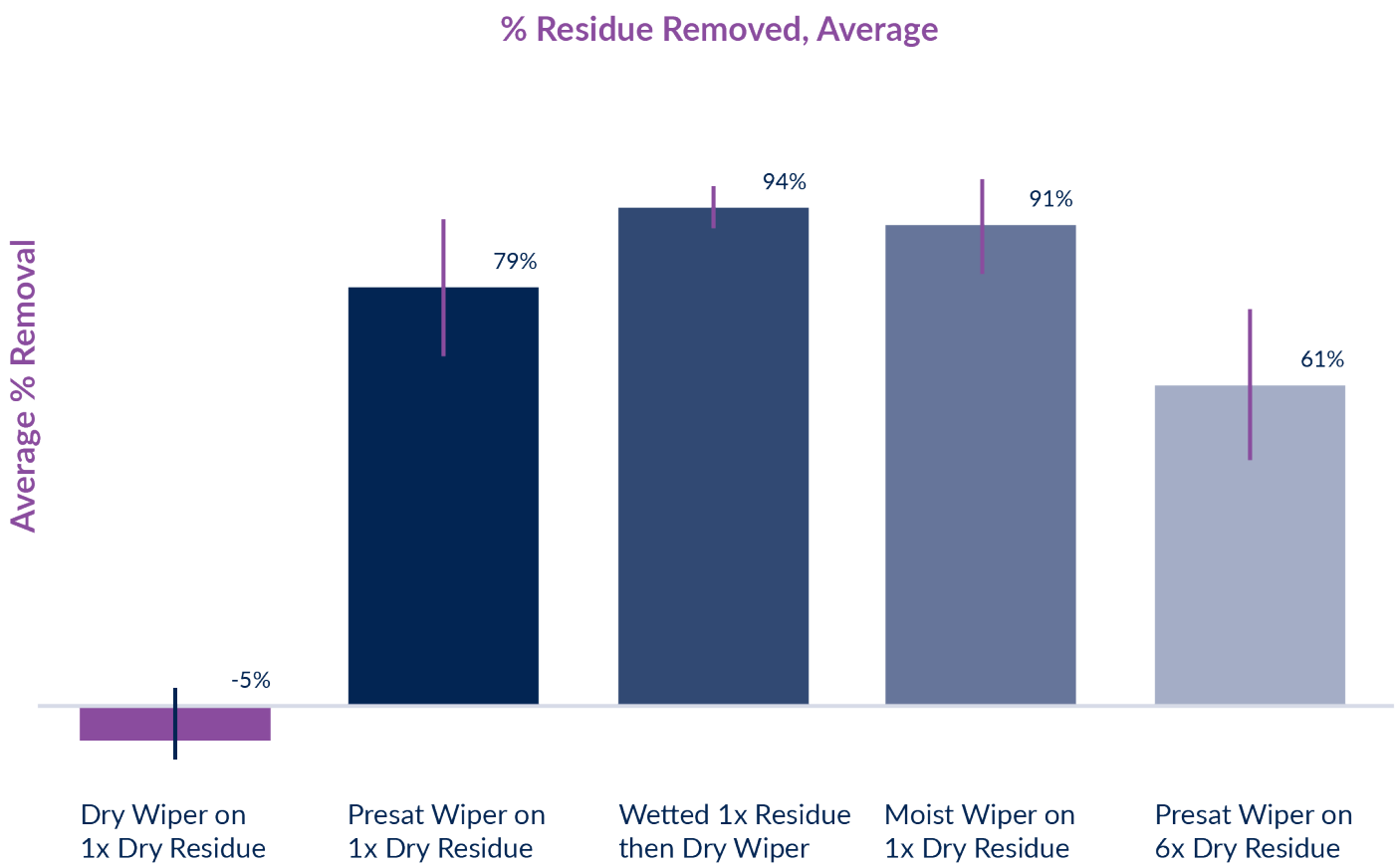


Table 2

DON'T LOSE YOUR COOL OVER COMPLIANCE

Annex 1 is here! We hope you are not "losing your cool".

Compliance is important to us too, so we're here to help you understand and implement the changes that affect your cleaning and disinfection protocols.

Contec have a choice of fast acting sporicides, free-rinsing disinfectants and a low residue detergent that can help you meet the new requirements. Our experienced team of microbiologists and technical experts are on hand to support with your Contamination Control Strategy, Disinfectant Selection and Validation or Residue Management.

For more information about Annex 1, your contamination control strategy or our range of suitable cleanroom products, visit vwr.com/contec

Clean counts most

CONTEC® CLEANROOM

Environmentally Preferable Production Supplies from Avantor®

Make every day Earth Day

Protecting the health, safety and welfare of your people and the integrity of your processes is always the priority, but looking after the future of our planet is also essential. At Avantor® we would like to help you make more sustainable product choices, so we have curated a selection of more environmentally friendly safety and cleanroom supplies and services. We are actively working with our manufacturing locations and key suppliers to add more products and services to this list.

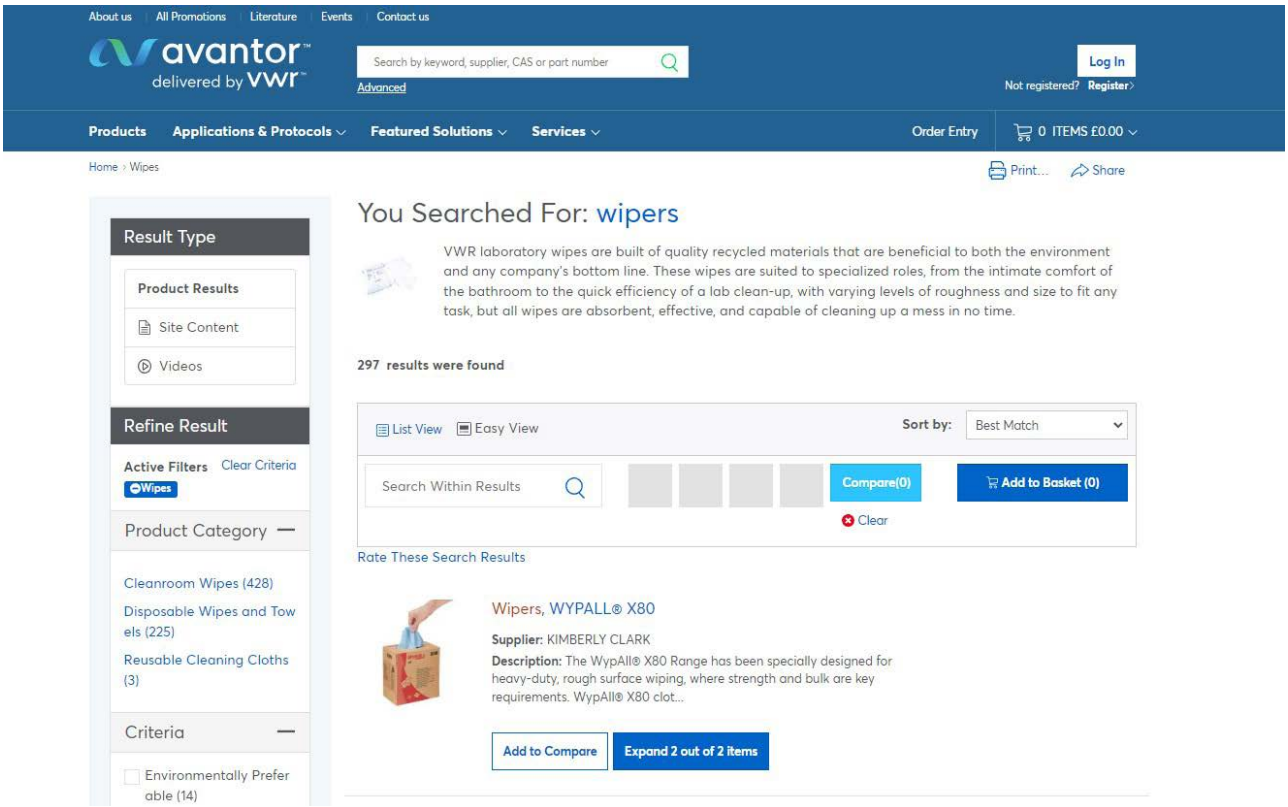
Together we can go green!

Visit our website:
https://www.vwr.com/sustainable_production_supplies

OUR ENVIRONMENTALLY PREFERABLE PRODUCT (EPP) METHODOLOGY

When we identify more environmentally preferable solutions, they are given an (EPP) green leaf designation on our website, so they can be easily identified.

When searching for an article, you can filter to show those that are EPP.



Products must incorporate one or more of the attributes below to qualify for the EPP green leaf.

- Energy efficient
- Water efficient
- Waste reducing (uses less material, recyclable, reusable, compostable or refillable)
- Sustainable materials (>30% post-consumer, renewable or bio-based material)
- Low manufacturing impact (made with >50% renewable energy or 20% less water than standard)
- Safer human and environmental health (refrigerants, chemicals, solvents, low VOC, etc.)
- Sustainable packaging (100% recyclable, or made from >30% recycled or renewable content, no single-use plastics, no packaging)
- Product transparency and disclosure (has verified life cycle assessment (LCA), environmental product declaration (EPD), health product declaration (HPD), ACT label or other third party verified environmental impact assessment)

Verification by a government agency or recognised third party certification is also accepted. For example:

ACT Label
Biodegradable Products Institute (BPI)
BioPreferred
Blue Angel
California Air Resource Board (CARB)
CDPH Standard Method v1.1 2010
Cradle to Cradle Certified
Declare
EcoLogo
ENERGY STAR
EPEAT
EU Ecolabel
Forest Stewardship Council (FSC)
German AgBB
Global Recycled Standard
GreenCircle Certified
GREENGUARD
GreenScreen For Safer Chemicals
Green Seal
LEVEL by BIFMA
Nordic Ecolabel
NSF International Programme For The Endorsement Of Forest Certification
RoHS Compliant
Safer Choice
SCS Global Services
South Coast Air Quality Management District (SCAQMD)
Sustainable Forestry Initiative (SFI)
TCO Certified
WaterSense

Visit our 'Sustainable Solutions' web page to see the environmentally preferable solutions available now.
www.vwr.com/sustainable-production-supplies






TERRACYCLE ZERO WASTE BOX

Zero Waste Box™ from TerraCycle®

Zero Waste Box™ from TerraCycle®, available through Avantor®, is a complete and convenient brand neutral service. It includes the storage, shipping and recycling of many single-use safety and cleanroom items which aren't currently recyclable through conventional facilities, giving them a new life in a variety of forms.

The Zero Waste Box™ range has now been extended to include two new versions that recycle non hazardous waste and to collect any flexible packaging.

INDUSTRIAL SAFETY EQUIPMENT, ZERO WASTE BOX™

To recycle non hazardous waste including:

- Industrial safety helmets
- Hi-vis jackets
- Heavy-duty gloves
- Ear defenders
- Protective eyewear (goggles)
- Safety bump caps

LEARN MORE

PLASTIC PACKAGING, ZERO WASTE BOX™

To collect any flexible plastic packaging, carrier bags and shipping material including bubble wrap, airbags, shrink wrap, cushioning pallet liners and covers. Any hard / rigid plastic packaging and plastic containers.

LEARN MORE

HOW ARE THE DIFFERENT TYPES OF MATERIALS RECYCLED?

PLASTICS are separated by number, melted down and turned into pellets that can be moulded and extruded to produce new products.

METALS are separated by type and smelted into ingots for reuse.

GLASS is cleaned and sorted by colour for processing. It is then crushed and melted to be used in new glass products.

ORGANICS are composted or used in industrial and commercial fertilisers.

FIBRES will be hydro pulped to separate out wax or plastic. TerraCycle® will not landfill or incinerate any of the waste they receive.

With over a billion items of PPE distributed across the globe to maintain safe work environments, proactive steps need to be taken to reduce the resulting waste.

This recycling service also reduces the need to extract virgin materials and deplete resources for new production. This avoided impact is not small for the manufacture of an average product. Over 90% of the environmental impact comes from extracting and refining the raw materials from which it is made.

HOW IT WORKS

- **ORDER:** Place your order with Avantor®.
- **COLLECT:** Place your Zero Waste Box™ in a convenient location and dispose of the accepted waste in to the box.
- **RETURN:** Once full, seal your Zero Waste Box™ and return it to TerraCycle® using the pre-paid shipping label that is fixed at the back of the box.
- **RECYCLE:** The collected waste is sorted into relevant categories, then sent for processing and transformed into new products.

Your collected waste will find a second life as recycled materials, reducing the need to extract virgin materials and deplete resources.

- Service currently available in UK, France, Germany and the Netherlands
- Accepted waste type varies by region

Zero Waste Box™ is a complete and convenient brand neutral solution which includes the storage, shipping and recycling of a waste that isn't currently recycled through local councils or traditional recycling facilities.

For more information contact **Jenifer.jones@avantorsciences.com**

For more sustainable safety solutions go to **https://vwr.com/sustainable_production_supplies**

Understanding sustainability and the role glove manufactures should have

Environmental consciousness and sustainable practices have come to represent a growing and important aspect of doing business across industries, including the healthcare, medical devices and life science sector. These industries are adopting strategies to enable forward-thinking efforts and initiatives to ensure they can reduce their environmental impact and meet societal goals for sustainability and transparency.

WHAT IS SUSTAINABILITY TODAY?

While the word "Sustainability" is commonly used in relation to the environment, the United Nations definition, "Meeting the needs of the present, without compromising the ability of future generations to meet their own needs," speaks to a much broader concept. Sustainability is about creating meaningful economic, environmental and social value, today and in the future. Healthcare has a direct role in sustainability, referenced by the UN's Sustainable Development Goal 3: "Good health and well-being." The challenge for the healthcare industry is to achieve this goal while also having a positive impact on the other goals for people and the environment.

THE SIGNIFICANCE OF SUSTAINABLE PRACTICE IN MAKING MEDICAL DEVICES AND PERSONAL PROTECTIVE EQUIPMENT (PPE)

Shining a light on the manufacture of medical devices and PPE reveals the significance of thinking about sustainability. The healthcare and life science sectors currently consume a large number of single-use products every day. This makes these sectors intensive consumers of energy and resources and currently leads to significant quantities of waste. Some consumption is essential, for example, surgical, examination and PPE gloves are integral to hygiene and infection and contamination control. Glove manufacture is currently energy and water intensive. But with ambitious and action-oriented goals, glove manufacture can be decoupled from resource constraints and aligned with the low carbon economy.

TAKING MEASURABLE ACTION TOWARD SUSTAINABILITY

Companies like Mölnlycke Health Care, a leading global provider of high-quality healthcare solutions, have recognised the urgency of embracing sustainability and have made it a core component of their strategy. Sustainability for Mölnlycke comprises three focus areas: adopting a green mindset, including embracing the UN Paris Agreement objectives to reduce the effects of climate change; creating and maintaining value adding responsible relationships with all stakeholders from customers, to patients, employees to suppliers; and conducting business in an ethical and compliant manner[1].

Mölnlycke has recognised the opportunity to secure its future growth and competitiveness through the transition to a low-carbon economy and therefore measures its GHG emissions across its entire value chain (Scope 1, 2 and 3). Mölnlycke has committed to a reduction in its absolute Scope 1 and 2 GHG emissions by 50% by 2030, compared to the 2016 baseline, supported by a transition to 100% fossil-free electricity by the end of 2024 and continuous absolute energy consumption year-on-year reduction as well as fossil-free heat sources transaction. As Scope 3 GHG emissions cover more than 80% of its total emissions, the company has also set targets on its indirect activities, such as purchased goods and services, transportation, application and use of our products, and end-of-life. These targets have been submitted to the Science Based Targets initiative for validation mid June this year[1].

WORKING TOGETHER TO OPTIMISE GLOVES' ENVIRONMENTAL PERFORMANCE

Life Cycle Assessment (LCA) shapes the company's main approach to sustainability in product development. In 2022 a full third party verified Life Cycle Assessment

for the Biogel surgical glove range[2] showed that nearly half of the global warming potential of a pair of Biogel gloves comes from Mölnlycke's own manufacturing. Therefore, a key aspect of Mölnlycke's sustainability drive is making progress on energy intensity and kind, water management, waste and hazardous substance reduction and efficient manufacturing processes during the entire gloves production[1].

By replacing fossil or virgin raw materials with safe materials from renewable, recycled sources Mölnlcyke is futher reducing the environmental impact of its glove production and contributes to the preservation of natural resources. In the construction of the new gloves plant, inaugurated in September 2022, Mölnlycke has embedded sustainability through decision guiding principles, including optimisation of energy and water consumption measures[1]. Optimised operations, smarter equipment and buildings can also contribute to improved employees' safety and well-being.

At the other end of the life cycle, Mölnlycke has implemented rigorous waste management strategies in its manufacturing processes. The company has a zero waste-to-landfill target for all production to achieve by 2030. The production waste management programme aims to avoid the creation of waste in the first place while at the same time minimising waste to landfill by maximising reuse and recycling. Beyond Mölnlycke operations, there is a target to provide Mölnlycke-made products in >95% recyclable packaging by 2030 to minimise customer and end-user waste. By optimising production methods and recycling initiatives, Mölnlycke can help reduce the overall GHG footprint associated with glove manufacturing and promote the circular economy.[1]

At the heart of achieving these goals is the importance of transparency and collaboration. Engaging with stakeholders, including customers, suppliers and regulatory bodies, fosters a culture of sustainability and more importantly, enables the co-creation of solutions that deliver measurable sustainability improvements throughout the value chain.

SUSTAINABILITY LEADERSHIP: MORE THAN A BUZZWORD

Mölnlycke's sustainability vision is to transform its business to become a global leader in sustainable healthcare, while ensuring the highest standards of patient care.[1]

Sustainability is a key business driver for the company and integral to its operations and product offering. It is the driver for growth, innovation and productivity and an essential part of Mölnlycke's employee value proposition. Mölnlycke's sustainability performance is independently verified by business sustainability ratings organisations, such as EcoVadis or CDP, and accredited bodies that certify ISO compliance.[1]

Reference

1. More details are available on pages 7-18, 34-38, 47, 100 - 147of our Annual Report 2022 molnlycke_annual-report_2022_digital.pdf
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How to Start your Waste Reduction Journey

Five tips for a successful 'waste walk'

By Ashley Davis
Global Sustainability Manager, Kimberly-Clark Professional

One of the best ways to begin your waste reduction journey is to conduct a 'Waste Walk' or a series of Waste Walks, depending on the size of your organisation. A well-planned Waste Walk can help you determine the opportunities for optimising management of waste streams and figure out what can be diverted.

A Waste Walk, also known as a 'Gemba Walk' in the practice of Lean and Six Sigma, means taking the time to watch how a process is done and talking with those who do the job.

Here are five tips for a successful Waste Walk:

1. Visit your organisation's receiving area first. Why? Because you need to understand what is coming into your facility and where it's being used.

2. Map it out in advance. Don't view your Waste Walk as a casual stroll through your facility. A Waste Walk should be properly planned and supported by all stakeholders at the site.

3. Document key details. Someone should be on hand to capture key information including photos of your waste, collection points and shipping containers and to do this at different times throughout the day.

4. Make sure to observe and take note of the behaviour of personnel around waste management, waste and material flow throughout the site, the location of all collection bins, and disposal fees for waste tonnages.

5. Get leadership buy-in and stakeholder alignment. Leadership should be involved from the start on the scope of work and key waste contributors. Align on outcomes and set timelines for mapping out your waste reduction plan. End users should also be included since they will ultimately be involved in implementing your waste reduction plan.

What comes next? Once you have as much detail as possible from your Waste Walk, you can begin prioritising the work ahead. Make sure to assess the:

- Largest volumes of waste
- Largest valued materials
- Easiest solutions
- Most challenging solutions

After this, you need to determine solutions for your waste. If you have in-house experts in waste and recycling, lean on them to help you assess the composition of your materials and your waste streams as well as specific recycling solutions.

If not, try reaching out to a local waste management organisation for 'simple' waste such as paper, cardboard, and general waste. For other waste, such as rubber, PPE, electronics or polymers, you may need to find a waste consultant who specialises in diverting these more complex waste streams.

When choosing a waste and recycling management partner, you should ensure that they:

- Provide contracts with clearly outlined expectations
- Supply financial and compliance information
- Give you access to regular diversion data

Lastly, remember that a waste and recycling journey takes time. You can't get there all at once, nor can you do it alone. Choose partners who will assist you in your journey. This could include manufacturer-led initiatives for recycling certain consumables, such as PPE, and 'middle men' who will help provide your waste with a second life. Whatever you do, take your time, be thorough and choose reputable partners with a proven and verifiable track record of success.

Kimberly-Clark Professional™ offers such a recycling solution for Kimtech™ branded gloves and coveralls and gives previously hard-to-recycle waste a second life. For more information on The RightCycle™ Programme please visit: **https//www.vwr.com/rightcycle**

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Keystone designs and manufactures a comprehensive range of sterilisation products made from DuPont™ Tyvek® material, SMS and BioShield materials, which are used to wrap and protect machine parts from contamination after an autoclave sterilisation process. They also offer a range of cleanroom consumables such as GMP equipment covers, irradiated bucket liners, sterility maintenance covers, face masks and pens, which minimise contamination concerns, reduce costs and increase comfort.

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A leading pharmaceutical company was installing a new filling line at their manufacturing facility in Europe and realised that this was a good opportunity to identify new products and to develop new wrapping configurations for their machine part sterilisation process rather than tolerating the current imperfect procedures.

Some of their machine parts were very heavy and could easily puncture wrappings post-sterilisation. Some were quite awkward shapes with handles and protrusions, and some didn't dismantle easily and needed to be wrapped as one unit so finding the correct solutions was challenging.

Avantor® and Keystone can offer support to customers right across Europe and North America, so they visited the facility to assess the requirements, measure, discuss, design and then offer advice along with a product proposal.

With their own production facility in North America, Keystone can manufacture customised sizes and configurations with excellent durability, yet still offer low lead times, small MOQs and competitive prices.
The bespoke solutions proposed included three-dimensional covers for the more awkward shapes, elasticated covers for critical surfaces, additional closures or skirt portions to cover more of the machine parts and they offered self-sealing, bags made with DuPont™ Tyvek® material as the outer layer.

Having the right sized products with reliable durability and user-friendly closures can save both time and money operationally as there is less chance of puncturing or tearing, therefore fewer failed sterilisation cycles. Operators can load and unload more effectively, reducing contamination and making their job safer and more efficient.

The resulting process improvement was better from a validation standpoint and helped with the presentation of parts when rebuilding the filling line post-sterilisation. Due to the success at this site when operational, this customer collaborated with Keystone again and replicated the same processes at their North American location.

Are you having any challenges with machine part wrapping or protecting parts post-sterilisation? Or do you have a new requirement where you would like a tailored solution to ensure optimum efficiency? Contact your local Avantor cleanroom specialist, and together with Keystone, we can propose a solution that will meet your needs.

Going the distance – providing accelerator-free cleanroom glove protection

Working in a cleanroom can be characterised as a marathon, not a sprint. It's important the protective equipment worn, like gloves, is able to go the distance. Providing the necessary level of protection required, while ensuring one's ability to work for long periods of time without causing skin irritation is imperative.

While many industries have moved away from latex gloves, latex is not the only common glove allergy. Accelerators are often used as part of the cleanroom glove manufacturing process to help stabilise the raw materials to form a strong, elastic product.

These accelerators used to produce many non-latex gloves can cause Type IV allergies, also known as a hypersensitivity reaction. This is an inflammatory reaction the body produces when exposed to certain allergens or accelerants. Natural rubber or sulfur-based chemical accelerators in non-latex gloves can cause allergic contact dermatitis (a common Type IV allergy), resulting in a rash with bumps or blisters that can impact the ability of cleanroom staff to properly do their job. According to the Centers for Disease Control and Prevention (CDC), cases of contact dermatitis lead to an estimated annual cost exceeding $1 billion.

For a clinician who changes gloves each time they enter an exam room, this may not be an issue, but for cleanroom employees who need to wear the same pair of gloves for an extended period of time, a reaction to the chemical accelerators can build up, especially for those with Type IV allergies. In one study focused on healthcare workers with hand eczema, all who switched to accelerator free gloves improved their situation, and two thirds of patients were completely free of symptoms.

Natural rubber or sulfur-based chemical accelerators in non-latex gloves can cause allergic contact dermatitis (a common Type IV allergy), resulting in a rash with bumps or blisters that can impact the ability of cleanroom staff to properly do their job.

Similar to how glove manufacturers and healthcare systems adapted to meet the needs of those with latex allergies by providing latex-free products, manufacturers have developed cleanroom gloves to meet the needs of those with Type IV allergies and sensitivities to latex or chemical accelerators. Brands like HALYARD* have developed and offer accelerator-free cleanroom gloves with low dermatitis potential. These gloves provide the same level of protection as traditional cleanroom gloves – recommended for use in ISO Class 3 cleanroom environments or higher, providing effective barrier protection against chemical splash, microorganisms and viruses – while still allowing for the flexibility and comfort needed when being worn over long periods of time.

The work done in cleanrooms is important and highly specialised, and those working in this industry deserve gloves that reflect the work they are doing. Accelerator-free cleanroom gloves, like HALYARD* **PURE**ZERO* Nitrile Gloves, provide employees with the high level of barrier protection needed while reducing the risk of allergies and skin irritation; thus, allowing workers to focus on the job at hand, rather than what's on their hands.

Opportunities and challenges in cell and gene therapy development

Q&A with Dr. Ger Brophy, Executive Vice President, Biopharma Production, Avantor®

One of the most revolutionary trends driving the biopharmaceutical sector is cell and gene therapy. At its most basic definition, gene therapy (also called human gene transfer) is the therapeutic delivery of nucleic acid into a patient's cells as a drug to treat disease. According to documentation published in The Journal of Gene Medicine, as of November 2017 nearly 2,600 gene therapy clinical trials have been undertaken in 38 countries around the world.

We interviewed Dr. Ger Brophy, Executive Vice President, Biopharma Production at Avantor®, to get his perspective on this exciting segment of the bioprocessing industry. He is especially eager to work with innovative leaders, scientists and researchers in the industry who are seeking to explore and expand the potential for gene therapy.

There is a great deal of attention around a select number of approved cell and gene therapies for relatively small patient groups. Can you describe the most exciting benefits arising from these therapies?

I think it is a very exciting space, and we're seeing the number of trials grow. It's probably most exciting because of the technology's ability to impact patients' lives.

Yes, the numbers of patients are relatively small at this point in time, but that's to be expected. Many biopharma researchers and manufacturers started with smaller defined patient populations, and in particular those with pediatric relapse refractory acute lymphoblastic leukemia. That's partly because they wanted to deal with small populations that they understood well and, in many cases, that didn't really have many other options for treatments.

We're seeing these companies moving on now to larger populations — starting with leukemia, now lymphomas. From our perspective, a key goal would be finding a treatment for multiple myeloma. If those patients begin to see benefits from cell and gene therapies, I think the excitement will feel justified.

Scalability and manufacturability — that's the next question we will all be looking at. Can we manufacture cell and gene therapies at scale? If we can manufacture these treatments at scale, can we do so safely?

What are the real game-changers driving the progress with cell and gene therapy?

For the first time, people are talking about curing these dreadful diseases. We're seeing the patient's own immune system used to fight cancer. Many of the first patients treated for acute lymphoblastic leukemia, are thriving — four to six years later.

The game-changer here is that you are using the body's own systems, either from a cellular immune system or from the ability to repair and replace defective or missing genes. CAR-T cell therapy is arguably among the most personalised medicine one can consider. The patient's own T cells are extracted, modified, activated, expanded, purified and returned to that patient.

The promise of personalised medicine has been growing for a long time. We're actually beginning to see real, tangible effects from the molecular knowledge now that we have an understanding of how the disease develops and how the patient responds to it.

Tell us about the industry — what kind of companies are working today in cell and gene therapy, and do you think this will change?

Many of the early movers in cell and gene therapy were small biotech startups. In some cases, these treatments were supported by major hospital centers. Increasingly, we've all seen a greater interest by the major biopharma industry. Novartis was probably the biggest; it started the earliest, and was successful in getting approval for Kymriah. But in the last year, we've seen Kite being acquired by Gilead, Juno being acquired by Celgene, and other companies in China driving major strategic partnerships with major biopharma companies.

As companies of this size get involved, we expect they will leverage their increased breadth and depth to develop new labels, develop new trials and find ways to manufacture these therapies at scale.

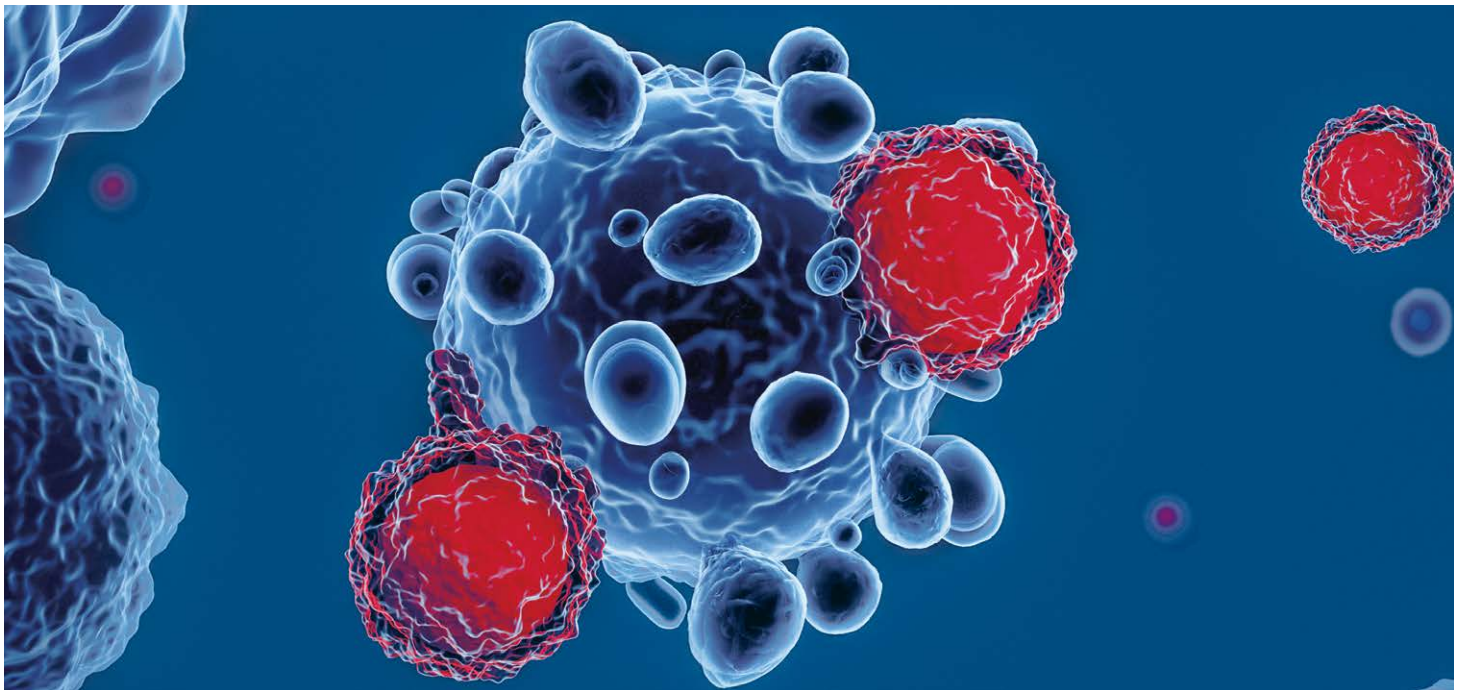
What are the critical challenges for companies working or going into this field?

Scalability and manufacturability — that's the next question we will all be looking at. Can we manufacture cell and gene therapies at scale? If we can manufacture these treatments at scale, can we do so safely? Can we do so at a reasonable cost so that the populations affected by these diseases can access treatments?

The issue is process standardisation. When you're talking about a cell therapy, the single biggest point of variability is the patient's own cells. And by its very nature, this is individual to the patient, and individual to the health of the patient at the time of leukapheresis.

Variables and failure modes have to be taken out of the process. We can standardise, close systems so that they're not exposed to failure modes, or miniaturise these systems — all this can help. We can improve technologies, like sterile fluid transfer, if we can use excipient technology to further stabilize and use analytical technology to understand what will make a successful or less successful therapy. We can increase the efficacy, decrease the risk and decrease the cost.

This is where Avantor® can help, since we supply cell-culture components, production chemicals and single-use technologies that aid in these processes. I think our knowledge – of cell culture, of technology development, sterile fluid transfer, fill and finish and excipients and the technology surrounding those – will be valuable and applicable to helping make these technologies available at scale.



How can companies react to those challenges? What are the tools or solutions they are looking for?

We need to better analyse and understand the variability that comes from the research data, even at the early stages of these trials, and use it to correlate to both clinical and process outcomes. Taking out manual steps as early as possible is going to be important, as well as creating closed systems using sterile fluid transfer technologies.

We need solutions around side effects, which is one of the most significant challenges. As we understand how to provide a more efficacious dose, perhaps using less cells, some of the side effects of these drug therapies may be improved.

And we must find scalable ways to address costs, which are far too high. The systems of reimbursement should be reviewed — for example, should reimbursement be made dependent on outcomes?

Ultimately, these drugs must be developed in a more cost-effective manner. That's an area where technology providers and suppliers, like our company and others, can play a significant role by closing and automating systems, and by understanding the contribution of labor and overhead and possible economies of scale from reducing processes.

A big issue for companies working in these therapies are the regulatory hurdles. What insights can you share about regulatory issues for cell and gene therapy?

I think the regulatory groups have been encouraging. To a degree, there's competition among different regional bodies – in Europe and in the UK, in China and in Japan, in different ways and within different specialties.

We have seen that regulatory bodies have been very open and collaborative in acknowledging that cell and gene therapy is different. They are willing to put into place the appropriate regulatory system to enable the drugs to get to market, and to monitor them going forward.

The FDA's support on CAR-T technologies is a good example. Regulators are allowing flexibility in the normal hierarchy of how clinical trials are performed, particularly in phase II and III trails, but the companies must still address the FDA's post-marketing commitments and safety issues.

With the amount of strong research into developing, understanding and characterising drug targets, and figuring out how to make these in production level volumes, this will be a constantly changing landscape. And, there will be many parts to patient treatment options going forward.

Do you think cell and gene therapy will be the core focus in the future for biopharma? Will it replace small molecules and biologics?

I don't think so. I think each type of drug product will find its niche. People tend to forget about small molecules, but they are still incredibly important in the market. Large molecules are also being developed for areas like neuro degeneration. I think they'll have a continued role to play there.

Monoclonals and biopharmaceuticals have only started to make a significant impact in the last 15 to 20 years. Cell and gene therapies are just starting and have yet to obviously make a significant market impact. With that considered, who's to say what's next?

With the amount of strong research into developing, understanding and characterising drug targets, and figuring out how to make these in production level volumes, this will be a constantly changing landscape. And, there will be many parts to patient treatment options going forward.

Avantor® is excited to be involved in this groundbreaking new space to treat some of the most complex and difficult diseases the world faces. It's clear that cell and gene therapy can succeed as one more healing tool — as with other treatments that moved from theoretical possibilities to real results, we can clearly see the issues that need to be addressed, and we're ready to help get the next stage of development in motion.

About the author

Dr. Ger Brophy is Executive Vice President, Biopharma Production. In his current role, Dr. Brophy is responsible for developing and implementing Avantor's Biopharma Production offering to support the current and future needs of our customers. Prior to joining Avantor, Dr. Brophy held a variety of research and development, strategy, advanced systems and business development positions with GE Healthcare Life Sciences, GE Healthcare Medical Diagnostics and Amersham for nearly 30 years. Dr. Brophy earned a Bachelor of Science in biotechnology, as well as a doctorate in molecular biology from Dublin City University in Ireland.

Solving cost and supply challenges in biopharma downstream processing

Dr. Nandu Deorkar, PhD., MBA, Senior Vice President,
Research & Development - Biopharma Production, Avantor®

Monoclonal antibodies (mAbs) are the dominant therapeutic modality in the biopharmaceutical industry, representing the largest sector of the market[1]. As of 2022, more than 100 mAb therapies have been approved by the FDA – over twice as many as had been approved only 5 years ago[2].

Behind the rapid rise and longstanding market dominance of mAbs are the high levels of specificity and affinity with which the pharmaceuticals bind to their targets, as well as the variety of therapeutic areas the biologics can address.

As the demand for mAbs and other therapeutic proteins has increased, so have concerns over cost and supply. Downstream processing – which accounts for roughly 60 percent of the cost of producing a biologic drug and often takes place over a period of weeks – is particularly challenging because it has not improved and scaled at the same rate as upstream processing has [3]. This is largely due to the complexity of downstream processing, which involves the movement of biological materials through a series of unit operations that include multiple chromatography steps. The complex stage presents numerous opportunities for improvement[3]. Of downstream processes, buffer management and chromatographic purification operations in particular are areas that are ripe for interventions to increase efficiency and scalability.

BUFFER MANAGEMENT

Buffers play a key role in chromatography purification steps in terms of both efficiency and purity. By stabilising the pH of a mixture, some buffers help proteins bind to ligands while others – called elution buffers – help to separate out byproducts. As the biomanufacturing industry moves toward

continuous bioprocessing and as titers resulting from upstream processes increase, the importance of and demand for buffers in downstream chromatography steps likewise continues to increase. Improving buffer efficacy and efficiency can happen in multiple ways, from optimising buffer management processes by selecting the appropriate formulation to improving buffer performance through the use of additives.

In-house buffer preparation has been the dominant choice for years[4]. Established methods for in-house buffer preparation, such as the use of WFI (water-for-injection)-grade water in the hydration of powdered buffers in steel tanks, are appropriate for generating large amounts of buffer. However, the large footprints and high amounts of labor required for such methods make buffer outsourcing an appealing option. Outsourcing buffer management often comes with the added benefit that the burden of ensuring quality and consistency in buffer materials is shifted to the supplier[5].

Though it remains practical to manage certain kinds of buffer preparation in-house, outsourcing offers significant benefits by reducing the necessary capital, labor and footprint and by ensuring scalability and a reliable supply chain. Alternatives to traditional buffer preparation methods include the procurement of hydrated buffers, delivered as ready-to-use buffer solutions or concentrated buffers, or pre-weighed, ready-to-use, powder supplied in Direct Dispense bags helping streamline the biopharma manufacturing process[4]. Beyond this, workflow improvements largely depend on buffer preparation method selected for a particular process or scale. Large-scale manufacturing – such as the production of mAbs, vaccines and recombinant proteins – and small-scale manufacturing – such as cell and gene therapy applications – have vastly different buffer needs, all of which can be accounted for through thoughtful collaboration between manufacturers and their suppliers.

The importance of this collaboration is demonstrated by the decision-making calculus involved in choosing between, for example, 1x buffers, buffer concentrates and buffer stocks. 1x buffers are ready-to-use and can be attached directly to the column. This ease of use, however, is balanced by concerns about the large amount of space such buffers require for storage. This is further complicated by the fact that some manufacturers, such as those developing new products, may not need enough buffer to justify the space and inventory issues generated by the use of 1x buffers.

For such manufacturers, multi-component buffer concentrates may make more sense. Those concentrates are intended to be used in conjunction with in-line dilution (ILD) skids. They reduce the warehouse space required compared to 1x buffers, but other issues arise. For example, multi-component concentrates tend not to generate cost savings, and the use of one concentrate in multiple process steps requires careful calculation and increases process complexity.

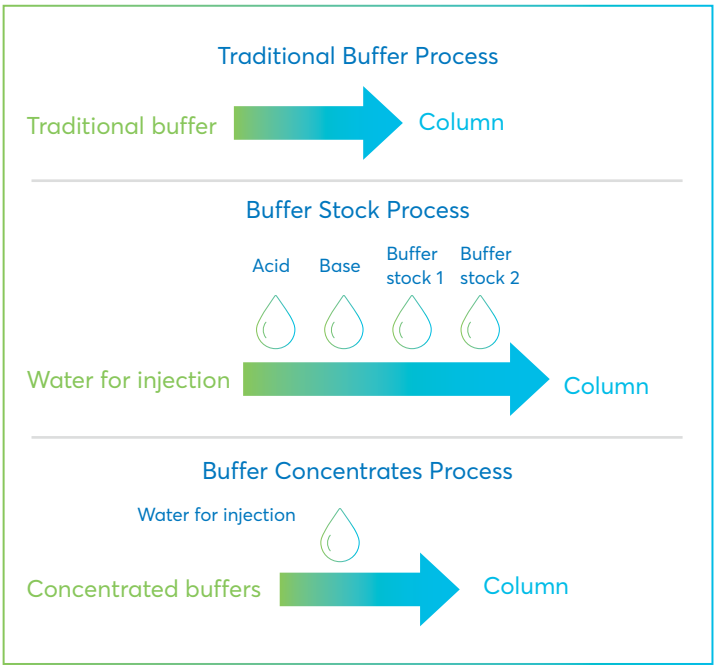


FIGURE 1. Buffer handling strategies using liquid raw materials process visual

Buffer stocks, single-component concentrates, are the most flexible of these three options, designed to be used in conjunction with WFI water, acids and bases in a buffer stock blending system. These single-component concentrates can be purchased in higher concentration preparations than multi-component buffer concentrates, and therefore require less space and minimise shipping costs. However, buffer stocks tend to require higher capital costs (see figure 1)[8].

The varied benefits and detriments of each of these buffer preparations can be most easily navigated with the help of a supplier with the process expertise to help their customer identify the optimal solutions for their workflow's needs.

Another area of interest for the enhancement of buffers used in chromatographic purification involves the use of additives that improve the retention of and selectivity for proteins in the chromatographic medium. For example, in hydrophobic interaction chromatography (HIC) – a common polishing step in monoclonal antibody purification processes – additives are used to modulate hydrophobic interactions and improve separation efficiency, which by extension improves throughput[3]. Similarly, additives might be employed to enhance the ability of elution buffers in affinity chromatography to dissociate bonds between proteins. The use of buffer additives, ready-to-use buffers and single-use fluid handling systems to enhance efficacy are still being fine-tuned, but the optimisation of the chemistry of chromatographic resins is showing itself to be one of the most effective ways to improve recovery while normalising or even reducing production costs[3].

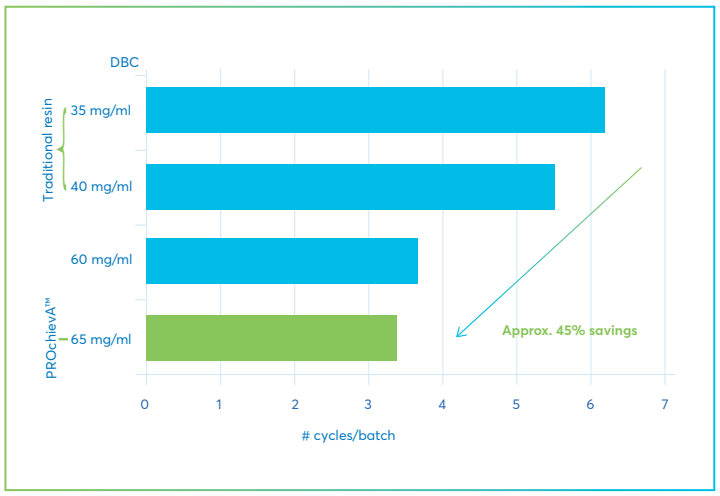


FIGURE 2. Effect of DBC on theoretical number of cycles per batch

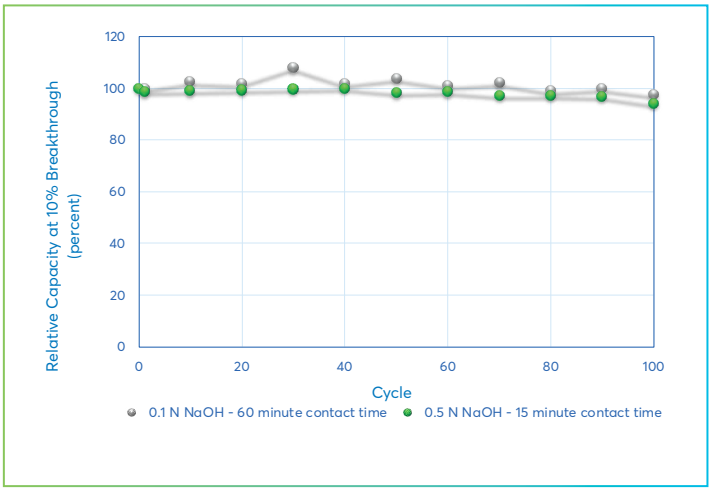


FIGURE 3. Resin life of PROchievA. All testing conducted at 2° C to 8° C.

CHROMATOGRAPHY

While the general improvement in upstream process titers in the biopharmaceutical industry is advantageous in many ways, it also burdens the downstream chromatographic steps that were originally designed to process smaller amounts of proteins[6]. Improved buffers are not enough to accommodate higher titers, so enhanced resins must also be part of an optimised downstream workflow.

Because of its near ubiquity in the downstream processing of antibody products, protein A affinity chromatography provides insight into potential improvements in the chromatographic aspects of the downstream processing of therapeutic proteins. For decades, protein A chromatography has been the gold standard for protein capture due to its specificity. This step alone provides up to 99% yield after capture [1]. However, protein A is expensive, and its frequent use leads to further expense in two ways. First, without thorough cleaning, impurities left in the column can interact with protein A and cause fouling. If harsh solutions are used to clean the columns, however, another challenge presents itself in the reduction of resin lifetime[6]. Furthermore, protein A ligands may leach from the resin, further increasing the purification burden on subsequent processing steps that are already overburdened due to the failure of downstream processes to improve at the same rate as upstream processes.

Multimodal or mixed-mode chromatography – in which ligands in the resin interact with the protein product in multiple ways – has gained attention as a way to optimise downstream chromatography steps in recent years. However, tailored ligands are perhaps the biggest recent change in the chromatographic purification of proteins[7]. Tailored ligands can significantly improve resin stability and selectivity and increase dynamic binding capacity, enabling resin to process more protein per cycle. For example, the J.T.Baker® BAKERBOND® PROchievA™ resin, a recombinant protein A affinity chromatography resin that uses a novel proprietary ligand, can reduce the number of cycles needed by 45% and the amount of buffer consumed by almost 40% (see figure 2)[6]. In addition to these significant performance boosts over traditional protein A affinity resins, BAKERBOND PROchievA has a high alkaline stability, which extends the resin lifetime even when the column is cleaned with sodium hydroxide (see figure 3)[6].

Tailored ligand-based resins, therefore, can significantly reduce process cost over time, especially with large batch sizes, through increased throughput and decreased resin and buffer consumption[6]. The high purity these resins achieve also reduces the burden on subsequent steps.

Finally, buffer management cannot truly be optimised without the implementation of quality support systems. Traditional sampling methods are destructive, risk contamination of buffer components and waste time. With side sampling and non-destructive identification technologies such as Raman ID compatible packaging, however, there is no need for physical sampling. This not only decreases risk but enables heightened operational efficiency[8].

DATA AGGREGATION AND THE FUTURE OF DOWNSTREAM PROCESSING

While the improvement of purification process materials like buffers and chromatography resins will be crucial for the continued alignment of downstream capabilities with upstream output, raw material availability is an issue that should not be ignored. Emerging technologies will enable biopharmaceutical companies to aggregate and analyse process data[9]. Having the resulting information available could allow companies to anticipate variations and understand their impact, minimising batch failures while heightening supply-chain visibility[9].

Because of this, even though real-time evaluation is not yet possible, emerging technologies that allow companies to monitor their processes and track raw material quality over time have the potential to inform process efficiencies and supply chain decisions. While the use of data to refine process parameters is a comparatively simple process involving batch repetition, characterising raw material variability involves the use of a variety of datasets. For example, the use of certificate of analysis data for all raw material lots manufactured, manufacturing in-process data, in-test actuals for conforming specs and stability testing interval data can enable biopharma manufacturers not only to assess but also to predict the performance of raw materials and therefore choose the most impactful workflow interventions[3].

In line with these opportunities, digital solutions can be developed that map the potential for variability in different raw materials and the potential impact of such variability. This is done through the aggregation and analysis of stability interval testing of downstream components. Though bringing this technology to bear in ways that can valuably inform process and materials decisions is difficult, it demonstrates the potential to minimise batch failures by increasing the understanding of variations' impacts.

CONCLUSION

Demand for therapeutic proteins has never been higher, and the biopharmaceutical companies and their raw materials' suppliers must collaborate effectively throughout the development and manufacturing processes for biologics. Cost control or even reduction, raw material availability, process efficiency and speed-to-market are all potential areas for improvement in the downstream processing of therapeutic proteins. While these goals may be obvious, their attainment is less so. The investigation of new, state-of-the-art materials will be crucial, but so will the development of process efficiencies and raw material solutions. Often, such solutions are dependent on the specific needs of a customer and their process, and providing data-driven solutions that best serve a workflow with the most efficient selections of raw materials and process improvements will necessitate a close relationship between those researching and producing therapeutic proteins and their downstream material suppliers. The resulting combination of knowledge–spanning insight into the precise needs of a particular product to expertise in process chemistries and raw material performance as well as supply chain issues and end-to-end workflow efficiencies–will be key to the generation of downstream solutions. This collaboration enables suppliers to meet their customers' needs for tailored solutions and high-quality materials, so that biologics producers can achieve the speed-to-market that today's biopharmaceutical industry demands.

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Failing to Plan is Planning to Fail:

The Case for Early Use of cGMP Raw Materials

Beth Kroeger-Fahnestock, Director, New Product Introduction, Avantor®

Insufficient planning, in the early stages of scale-up, results in an inefficient process at best, or validation failures leading to serious market delays at worst. Using cGMP grade reagents earlier in the transition to large-scale commercial manufacturing makes for a seamless transition — maintaining quality and viability while avoiding additional costs, potential process re-development and lost production time.

When you identify suppliers of higher quality reagents ahead of time — chemicals that have been extensively tested and documented — you gain heightened supply chain security and assurance of regulatory compliance. Use cGMP raw materials during development to:

- Minimise risk of contamination or aberrant results due to impurities
- Provide material traceability to support regulatory compliance
- Eliminate requalification of material due to unavailable grade and quantity of material after transfer
- Ensure product consistency that meets intended specifications

Current Good Manufacturing Practice (cGMP) regulations are set regionally, based on guidelines developed by organisations including the International Conference on Harmonisation (ICH), Pharmaceutical Inspection Convention/ Pharmaceutical Inspection Co-operation Scheme (PIC/S), and regulatory agencies. They focus on preventing cross-contamination and keeping environmental contaminants out of the product, thereby simultaneously protecting the end user and the product. There is no cGMP certification; they are standards to maintain quality and purity characteristics in pharmaceutical development.

QUALITY: INDUSTRIAL AND LAB-GRADE REAGENTS DO NOT GUARANTEE CRITICAL PERFORMANCE SPECIFICATIONS

The reagents needed for clinical manufacturing must meet additional regulatory and testing requirements to validate sterility, consistency and efficacy. This includes more quality control testing of initial raw materials, more in-depth documentation to show manufacturing control and validated manufacturing and cleaning processes to minimise risk of product failure and subsequently, patient safety due to variability or contamination.

KEY CHALLENGES

- **Lot release testing.** Research use only (RUO) raw materials (and equipment) do not include comprehensive — and time-consuming — QC testing, specifically for endotoxins and particulates leading to patient safety concerns
- **Sterility validation.** With the change to GMP products, this is not a 'one and done' test validation; dose audits must be done regularly to prove sterility
- **Clinical comparability studies**. Time-consuming clinical comparability studies to prove the raw material changes do not alter the final product. By making the change early, you get less chance of variants or atypicals and that validation will fail

WHAT WE OFFER

- Regulatory and quality systems and history of supporting customers with regulatory submissions
- Quality audits with Rx-360 available to license
- Certified ISO 9001 and ISO 13485 quality systems
- Animal origin-free or EMA/410/01 compliant materials
- Sterility validation per ANSI/AAMI/ISO 11137 (VDmax25)
- Sterile barrier shelf life validation per ANSI/AAMI/ISO 11607
- BPOG standardised extractables testing protocol
- Endotoxin USP <85> and particulate USP <788> lot release testing
- Lot-to-lot consistency and comprehensive supportive testing
- Custom specifications and performance characteristics available

DOCUMENTATION: LACK OF DOCUMENTATION SUPPORT CAN LEAD TO DELAYS OR REJECTIONS

Documentation serves as a record that a supplier's manufacturing facility, processes, and operators are fully qualified. It is not a box to be checked, but should be a systematic approach to acquiring, analysing, storing and disseminating information related to products, manufacturing processes and components. (ICH Q10).

KEY CHALLENGES

- **Process validation**. Supporting documentation should be in place for scale-up. If you wait, you lose time in getting necessary documentation
- **Traceability.** Raw materials at this level must be documented and traceable. This ensures any issues with end product or process can be adequately investigated and ruled out
- **Certified quality systems.** Documentation is not a stand-alone deliverable. These change with the transition from RUO to cGMP, as do corrective/preventative actions and documentation requirements

WHAT WE OFFER

- Certificates of Conformance, Quality or Analysis are available with SDS documents online
- Equipment Cleaning and Use Record (6.2)
- Records of Raw Materials, Intermediates, API Labelling and Packaging Materials (6.3)
- Master Production Instructions (Master Production and Control Records) (6.4)
- Batch Production Records (Batch Production and Control Records) (6.5) and Review (6.7); our knowledge of regional differences facilitate regulatory compliance
- Laboratory Control Records (6.6)
- Supply chain statements
- Rigorous documentation of deviations along with root cause analysis and corrective/preventative actions

SUPPLY: REAGENTS THAT ARE UNAVAILABLE CAUSE DISRUPTIVE CHANGES AND/OR STOCKOUTS

Collaborative planning, smart forecasting and sales and operation planning are needed to keep your cGMP materials in stock to hit your manufacturing goals. Establishing as early as possible, a comprehensive supply chain strategy, as well as a robust management of change programme will help mitigate risks.

KEY CHALLENGES

- **Change management.** Change controls become burdensome in full GMP systems; materials that worked for one workflow may not work for another
- **Limited raw materials list**. Key to building a diverse and largely approved raw material parts list ahead of time, so a stable supply chain is in place with qualified secondary suppliers in case a reagent is discontinued
- **New production/distribution sites**. Moving manufacturing can disrupt a previously secure supply of cGMP reagents; facilities must be certified. Changing the source of supply of critical raw materials requires adherence to formal change control system
- **Supplier auditing**. A system for evaluating suppliers of critical materials as necessary; all cGMP production materials must be traceable

WHAT WE OFFER

- Collaborative planning, forecasting and replenishment (CPFR): We provide service level reports on assurance of supply through our Critical Materials Care team
- A formal Management of Change (MOC) programme and change notification services for supply consistency and transparency
- Certified global cGMP and cGDP facilities; with local field-based support on three continents
- Supplier auditing and integrity provides proactive, risk-based audits that enable us to understand the capabilities of new suppliers and collaborate effectively to promptly address CAPA if needed
- Largest qualified portfolio of premium products and chemicals

Why Choose Avantor®?

Trust chemicals and excipients from Avantor to help you reach the market faster with new biologics. With our global network of cGMP and cGDP manufacturing facilities, customer-centric quality programmes, comprehensive management of change system and in-depth industry expertise, Avantor can help you improve your production process performance, increase product yield and comply with regulatory requirements.

Effective Residue Removal
A Critical Step in Cleaning Strategy

CLEANING MATERIALS MATTER

The type of cleaning solutions and materials used for residue removal is a key to effective removal of dirt and debris, as well as the minimisation of residue that may be left behind by detergents and fabrics.

The chart data compares the effectiveness of Micronova NovaClean™ 'all purpose' cleanroom detergent to a typically used 70% IPA solution using Micronova cleanroom fabrics (recommended for ISO 5 to 9 cleanrooms) compared to a generic, 100% polyester wipe (control). These materials were tested by using each to remove the dried surface residue of a 5000 parts per million (ppm) sodium hypochlorite (bleach) solution and the residue from a disinfectant.

CLEAN COMPARISONS

The results of the fabric comparison show microfibre – a highly absorbent, slightly tufted, 80% polyester, 20% nylon fabric – to be twice as effective in removing surface residue as a generic control fabric. Microfiber with PolyMesh - a microfibre fabric with a layer of polyester braid, also removed a significant amount of the visual residue with its added scrubbing factor. NovaScrub - a durable open-pore reticulated foam, excelled at loosening the dried residue. Refer to the table for more results.

In comparing the cleaning solutions, the average result for each fabric showed a significantly lower level of visible residue when NovaClean is used compared to 70% IPA. Again, the Microfiber fabric boasts the best results with 0% visible residue, compared to 12% using IPA. This is why detergents with surfactants that dislodge residues and debris, while leaving minimal residue of their own, are preferred when cleaning. NovaClean is filtered to 0,1 µm, with metals and common salt ions in the parts per billion (ppb) range. It cleans surfaces effectively without leaving significant residue.

The last comparison shows the effectiveness of NovaClean detergent compared to deionised (DI) water to remove the visible residue of a standard quaternary ammonium disinfectant. The polyester control fabric combined with DI water only removed about 50% of the disinfectant residue, compared to 75% removed when using NovaClean as the solution.

RECOMMENDATIONS

When devising a plan for residue removal, consider the type of residue, the fabric material and the solution content and residuals. Tufted fabrics, like Micronova Microfiber fabric, work well at eliminating both salt and solution residues, and NovaClean detergent is superior to DI water and IPA for removing dirt and debris, as well as residue from other solutions.

	Average visible residue after wiping	
Fabric used for wiping	0.5% (v/v) sodium hypochlorite (5000 ppm) residue remaining when using 70% IPA	1.6% (v/v) quaternary ammonium disinfectant residue remaining when using NovaClean
Control fabric: 100% polyester	25%	25%
MicroFiber: 80% polyester, 20% polyamide	12,5%	0%
MicroFiber with PolyMesh, braided polyester mesh layer	17,5%	15%
NovaScrub: Polyether, reticulated dry foam	25%	25%
PolySorb: 100% textured polyester	30%	10%
MegaTex: 100% textured polyamide	42,5%	15%
PolyMesh: Braided mesh over 100% knit polyester	30%	15%

	1,6% (v/v) quaternary ammonium disinfectant residue using control fabric	
Fabric	**DI water**	**NovaClean detergent**
Control fabric: 100% polyester	50%	25%
	50% residue reduction when NovaClean is used.	

Description	Size	Packaging	Pk	Cat. No.
NovaClean™ 'all purpose' cleanroom detergent	950 ml	Spray bottle	1	**115-0290**
NovaClean™ 'all purpose' cleanroom detergent	3800 ml	Concentrate refill	1	**115-0289**
SnapMop™ snap-on flat head mop cover	360 mm length		1	**129-0975**
MicroFiber wipe	229×229 mm		10	**129-3812**
MicroFiber cleaning mitt	305 mm length		1	**129-0617**

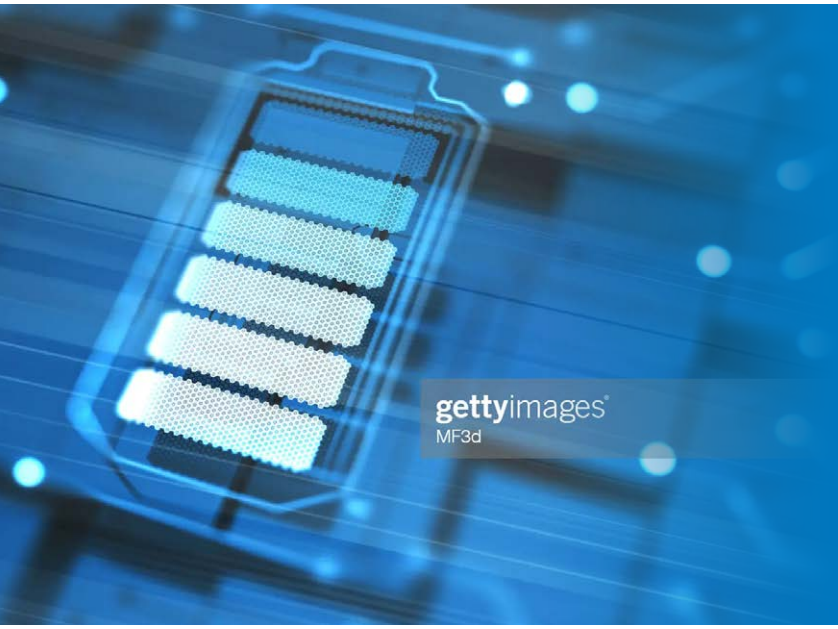
Residue Removal at its Most Efficient

NovaClean™ All Purpose Cleanroom Detergent and MicroFiber Fabric

Remove all types of residues, without contaminating with cleaning materials

- NovaClean is filtered to 0,1 µm, with metals and common salt ions in ppb
- Surfactants easily dislodge residues and debris without excess scrubbing
- Cleans surfaces effectively without leaving significant residue
- MicroFiber is highly absorbent, slightly tufted, 80% polyester, 20% nylon fabric

Avantor® for Advanced Battery Science and Technology



Innovation in battery technology is becoming vital to facilitate energy transition. Avantor now supports customers active in research and development, also production and recycling of advanced batteries.

Avantor is setting battery science in motion to create a better world.

"We are the trusted global partner to customers enabling transformation of advanced battery science, supporting the entire value chain by offering a broad portfolio of high quality products and tailored services through a single supplier partner."

Advanced Battery Science and Technology

Learn more

avantor™

Artificial Intelligence Driving Inventory Management for improved single-use systems manufacturing

Equally important to the manufacturing process of SU products is ensuring the proper inventory of the associated packaging, including primary packaging bags, labels and boxes.

Single-use manufacturers need powerful inventory management, production forecasting and control tools that will support the flexibility and certainty they need to be agile and responsive suppliers for biopharma customers with needs that are constantly evolving.

BUILDING AND PROVIDING VALUE WITH THE LARGEST "LIBRARY"

SU manufacturers are true systems integrators; the final SU product or assembly is designed for a specific customer's use, built from the specified connectors, tubing, bottles and other raw material components designed for their unique upstream or downstream process function. All raw materials that go into the production of the final assembly are part of the raw material "library." Every part that is included in the library has been carefully selected and evaluated for its regulatory requirements and specifications. These specifications include (but are not limited to) USP Class VI, gamma stability, ADCF, chemical compatibility, supply assurance, etc.

FIGURE 1: Examples of SU libraries of material and examples of the assemblies they produce.

Growing Raw Materials Libraries

- Connectors
- Filters
- Film
- Tubing
- Conical Tubes

Finished Assemblies

- Tubesets
- Bottle Assemblies
- Bioprocess Bags
- Sampling
- Assemblies

Avantor® has built and continues to expand their sophisticated library of SU raw material supplies, as well as direct, fast-moving items such as boxes, fasteners, PPE gowns and other materials, to enable efficient SU production. If an existing SU assembly needs to be modified to include a different filter (due to changes in upstream production or batch sizes), Avantor can access its library to modify the filtration without having to do extensive testing or validation of the entire design.

This library is also an agile production tool to ensure that high-moving cleanroom and packaging items are also stocked and available, based on the current and upcoming production schedules. This library approach provides a powerful foundation for true end-to-end SU manufacturing, covering the entire lifecycle of the product.

In addition, investing the time and resources to expand it and keep it up to date gives Avantor the ability to match the innovations and improvements its customers are making as they advance biologic production processes.

MAJOR SU INVENTORY AND SUPPLY CHAIN ISSUES

Building and sustaining the inventory and supply chain resources necessary for productive and agile SU manufacturing is forcing SU providers to solve several interrelated issues.

The first is common to many life sciences lab operations, as well as manufacturers in other industries: lack of complete, real-time visibility into inventory of both SU raw materials and production-related materials. There are many state-of-the-art inventory management platforms that can, if properly established and with proper inventory control, provide the inventory visibility SU manufacturers need to have, especially with the demands for regulatory compliance and customisation called for with SU technology.

Secondly, single-use manufacturers continue to be challenged with unpredictable supply chains. The impact of COVID on global supply chains and lingering inefficiencies for critical components have led many manufacturers to adopt less efficient and expensive "just in case" overordering and supply hoarding practices.

While adding some elasticity to the supply chain instead of relying on extremely tight just-in-time ordering and inventory management practices makes sense, there are ways to make much more effective use of advanced inventory management and forecasting tools that use machine learning and artificial intelligence (AI) capabilities.

Ultimately, lack of visibility and unpredictable supply chains can limit a SU manufacturer's unique value to biopharma producers: the ability to rapidly create custom designs and fill orders for SU products that can help advance biopharma innovation and productivity.

SOLUTION: LEVERAGE AI FOR DATA-DRIVEN DECISION MAKING

Taken on a piecemeal basis, even the most robust inventory manager software can still have gaps in information that will inhibit the ability of SU manufacturers to be as agile and responsive as they need to be to help advance biopharma productivity.

There is a growing recognition that the use of AI and machine learning tools can begin the process of moving from predictive, human-driven inventory management and manufacturing processes to genuine, data-driven decision making that goes beyond predicting what is needed to determining, prescribing and essentially deciding how to leverage the supply chain and nearly perfectly match it with the SU product demand.

From predictive to prescriptive

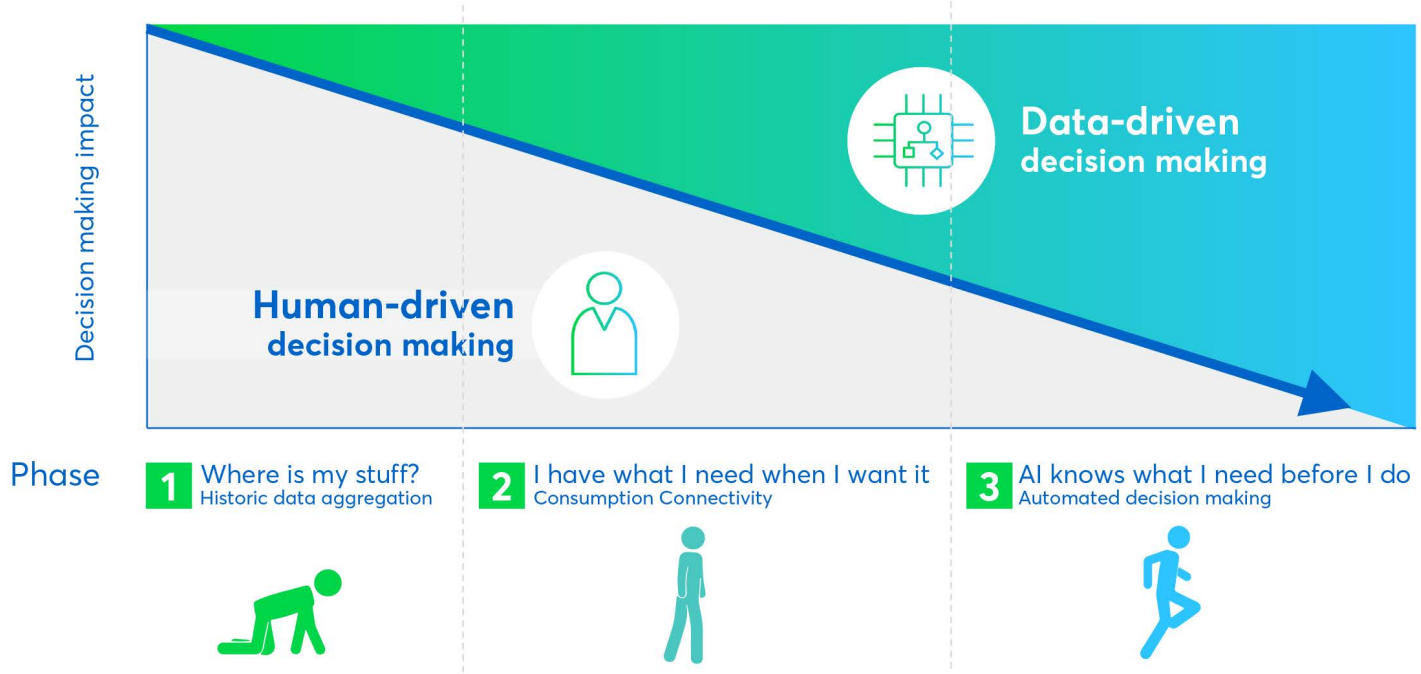


FIGURE 1: Three key stages moving from predictive to AI-driven prescriptive decision making.

With AI and machine learning, SU manufacturers have stronger tools to automate and proactively identify deficits or roadblocks in both onsite inventories and supply chain resources. This can be done through the use of newly available inventory tracking tools like smart shelves that use Internet of Things technology to gather critical, real-time data.

This cuts down the time and effort required by sending personnel to manually scan shelves or double-check storage areas to track down materials that are supposed to be in stock. With AI learning and tracking what's available — and what isn't — production planning and inventory restocking becomes prescriptive; order replenishment can even be automated.

Biopharmaceutical manufacturers have launched significant investments in AI and advanced data mining capabilities. These companies are designing their own technology and partnering with AI platform developers for support in target identification, drug design and clinical trial analysis.[3]

It makes sense, then, with the expanded role SU technology is playing in biopharma, for SU manufacturers to consider making similar investments. The ultimate vision is to go from where many SU manufacturers are now — historic data aggregation, or "where is my stuff?" — to automated decision making, or "AI knows what I need before I do."

CASE STUDY: IMPLEMENTING AI IN SU MANUFACTURING

At Avantor Fluid Handling (AFH), expanding the role of AI technology to move from predictive to prescriptive decision making has been following the multistage model. AFH is building from existing historic data aggregation processes to a more advanced consumption connectivity operation with improved confidence in real-time inventory availability and operational efficiency, with the ultimate goal of automated data driven decisions.

There are two factors that are key to helping move this implementation forward:

– Collaboration with customers: AFH has established close working relationships with drug manufacturers using SU technology. These relationships have been critical to helping AFH understand and respond to fast-emerging changes in SU product requirements.

These close collaborations enable AFH to take maximum advantage of Avantor's best-in-class library approach to SU technology manufacturing. This approach lets SU end users choose from a wide selection of single-use raw materials from Avantor's brands or other vendors. To fully realise the agility this open architecture approach offers, AFH has to have the confidence that its inventory and supply chain can meet a request for a new assembly.

– Expanding the use of IoT technology: Data-driven decisions need as much data, in real time, to make effective choices that manufacturers trust. At AFH, a significant investment in a range of IoT systems is generating that data, not only to guide current decision making (not yet fully automated) but also to build up deep historic data that AI technology can mine to enable reaching the ultimate goals of automated decision making.

The technology has enabled AFH to develop a more sophisticated approach to managing its SU component inventory. Using a multitiered approach, components are identified and managed according to criticality: Highly critical, moderate or low-level.

Based on the data they have already accumulated, critical components are those with longer lead times and with fewer sources in the supply chain that provide that component. Using this approach, AFH is also able to work multiple layers of opportunity based on an end user's regulatory requirements. These efforts were expanded during the COVID pandemic and enabled the implementation of stronger supply chain assurance and improved business continuity capabilities.

The portfolio of IoT technologies developed by Avantor and deployed at AFH's Devens, Massachusetts, manufacturing facility is already having a major impact on the facility's efficiency, quality control and ability to meet customer requirements.

Smart buttons:
These simple devices support the digitisation of cleanroom processes, enabling significant time savings. Located throughout the workspace, they can be used by personnel to request quality control (QC) or engineering support from outside the cleanroom. They have already contributed to improving throughput during assembly processes while increasing assurance that all critical QC inspections are conducted before an assembly can move to the next step in the process, either to complete assembly or send to packaging.

The smart buttons provide a single point of contact for onsite support teams, further standardising the process. Equally important, better management of these kinds of technical requests is helping minimise the frequency with which personnel have to enter the controlled environment, helping reduce contamination risks.

Over the long term, machine learning can track when and why these requests were made and correlate with other dataflows to identify ways to further streamline processes, potentially even automating support requests based on the long-term data captured.

Smart shelves:
These tools are crucial to transforming SU inventory management. The real-time data they provide contributes to building the critical insight AI needs to learn and ultimately prescribe order and replenishment cycles, guided by the AFH's criticality approach to component supplies combined with more enriched data from Avantor's global supply chain.

Smart shelves developed by Avantor and used in Devens are dramatically improving inventory visibility, helping minimise inventory discrepancies, reducing stockouts and generating detailed consumption data.

The data generated is fully integrated with ERP systems and is already supporting automated reordering. This includes more than just SU components: High-volume inventory items such as PPE products, as well as all the packaging materials needed for safe, aseptic shipping of complete SU assemblies, are tracked and managed through tools like smart shelves.

They are also generating significant labor savings by significantly reducing the need to have personnel inspect and scan shelved inventory to update and verify stock availability. This means the Devens team can assign personnel to more important, value added SU production tasks, often saving hours of time each week previously dedicated to double-checking what's on hand.

AI-powered vision systems:
Implementing an array of vision systems, both in storage areas and in cleanrooms where SU products are assembled, can significantly improve quality monitoring and control, especially related to the proper use of PPE materials, as well as critical QC monitoring of SU assembly steps.

In SU production, there is a significant amount of time embedded in product inspection and assembly verification — such as seal inspections — as well as verification that associates are properly gowned with the correct PPE before proceeding into the cleanroom. Through AI-driven vision systems, quality and specification assurance can provide critical backups through proactive deviation alerts if there has been an error in these steps.

Vision systems can combine with data from smart shelves to enhance inventory management, tracking and replenishment processes. They also can contribute to AI efforts to harness data to better understand when and how errors in assembly and gowning procedures occur and help fuel prescriptive end user, inventory and market forecasting.

MOVING SU MANUFACTURING FORWARD WITH AI

Demand for single-use systems and technology in biopharma will continue to grow, challenging SU manufacturers to be more productive as well as more agile, to satisfy the customisation requirements that many drug producers will have as they continue to innovate their manufacturing processes.

AI-driven inventory management for the full range of SU products and manufacturing needs — components, PPE, packaging materials and other items — provides a powerful tool to enable SU manufacturers to meet this demand.

Advances in AI and machine learning systems, coupled with sophisticated IoT systems such as smart shelves and vision systems, can generate the data needed to move inventory management from predictive to prescriptive decision making.

At Avantor Fluid Handling, these tools and the investment in building AI-driven decision making are already generating tangible savings and greater efficiencies in production and quality control. Combined with Avantor's library approach to inventory management, there are significant advantages to investing in both the IoT technology Avantor offers and the implementation of AI capabilities to elevate SU manufacturing productivity.

With these tools, SU manufacturers will spend less time "checking the shelves" and devote more time and expert resources to the scientific and engineering challenges of developing innovative new SU solutions for bioprocess drug manufacturers.

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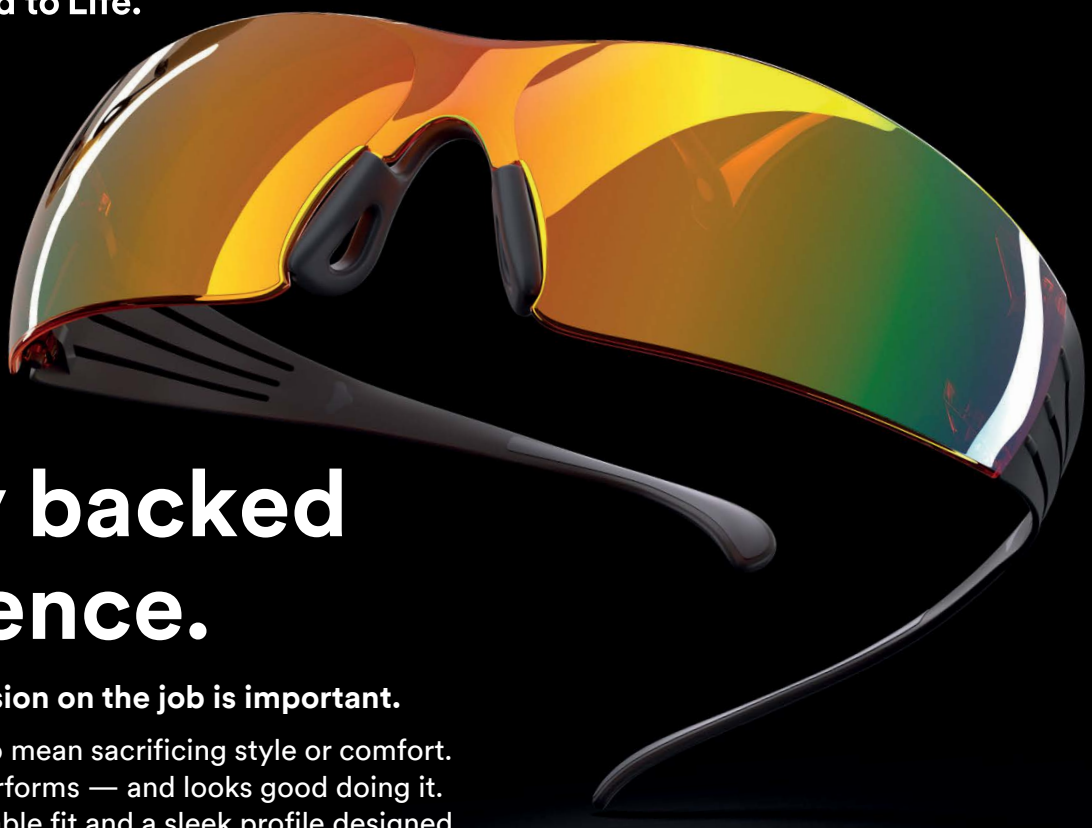
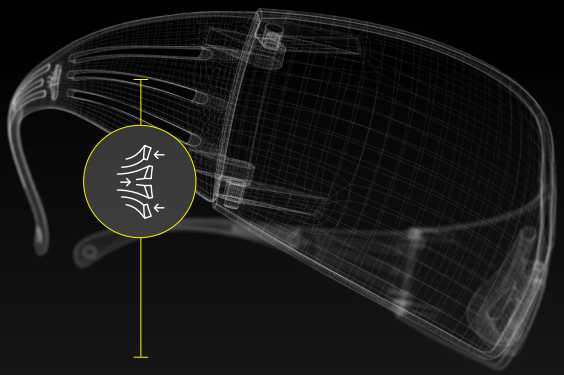


Safety backed by science.

Protecting your vision on the job is important.

But it doesn't have to mean sacrificing style or comfort. Get eyewear that performs — and looks good doing it. Featuring a comfortable fit and a sleek profile designed to work with other personal protective equipment, 3M™ SecureFit™ Safety Glasses helps keep you safe and comfortable on the job.



3M™ Pressure Diffusion Temple Technology.

3M's innovative temple design features slotted ribs that provide comfortable pressure equalisation, allowing the temples to flex and self-adjust to the size and shape of the wearer's head. Regardless of head size, from small heads to large heads, this technology is designed to provide a secure and comfortable fit for an extended period of wear time.

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The newest family members are the 100 Series, providing sleek, comfortable eye protection at an economical price and the 500 Series, featuring a contemporary lens design with adjustable ratcheting temples for a more personalised fit.

View the range

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Know exactly where your consumables are with the next generation of Inventory Manager. From visibility with no surprises to reporting you can access anytime, anywhere, our updated platform brings the Lab of the Future right to your bench. Get ready to optimise consumables management, so you worry less about overstocks and stockouts — and focus more on what you do best: **life-changing science**.

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Safety Inside - Your Safety is Crucial

We combine ingenious products and packaging solutions with individual support to keep you safe, simplify your lab work, and help you save resources. Discover some safety aspects with risk prevention and emergency solutions that match your high standards.

Risk prevention – protect yourself

Preventing harm starts with the right packaging and chemicals. Merck offers 350 years of experience in handling and designing packaging for hazardous goods, so you can enjoy unrivalled safety standards and application-oriented foresight. Our specially developed packaging materials ensure you work safely even during critical applications.

Acids in Safebreak Bottles

SAFETY AND HIGH QUALITY FROM THE SAME BOTTLE!

LABORATORY ISSUES

Glass bottles have very long, useful lives. As containers for all manner of chemicals, they remain a valuable inert material for everyday use in the laboratory. Yet, however much care is taken, breakage does occur. It is something that simply has to reckoned with. Serious injury, contamination or consequential damage can be the result. You can avoid it with us!

OUR SOLUTION

All of our experience in dealing with the hazard potential of acids in glass bottles has been incorporated in the specifications of the new 'Safebreak' bottle, the safest safety bottle!

'Safebreak' is a glass bottle coated with polyethylene. Should the bottle fall and break, the liquid and glass splinters are reliably retained within the polyethylene coating. Each Safebreak bottle is fitted with a S40 screw cap made of polyethylene but with an integrated PTFE component. This cap renders the bottle absolutely airtight so that no liquid or vapour can escape.

BENEFITS FOR YOU

The computer designed, exclusive Safebreak bottle combines all the advantages in one: It meets all safety requirements and it ensures that the customer receives exactly the same quality of content as that dispatched from us. It can be incorporated in all logistic systems.

The Safebreak bottle withstands considerable impact force. Should a breakage occur, the acid and any glass splinters can be reliably contained, and the user cannot be injured by escaping acid. Even after frequent opening and closing, the screw cap remains perfectly intact so that the environment is protected from leakage and contamination. The bottle can be easily and ecologically disposed of and recycled, just as the conventional glass bottle, and the PE is burnt off without affecting the environment. Hence, they are safer for you and the planet.

FIND OUR PRODUCTS HERE : 

Take Full Control with One Hand

NEW 1 L HDPE BOTTLE AND POPULAR 2,5 L HDPE BOTTLE FOR ACIDS, BASES AND SOLVENTS

- Moulded for hands. Made for handiness. Safe and simple handling of hazardous liquids is key to protecting personnel from accidents and health risks. That's why we created the new 'easy grip' 1 L HDPE bottle. Just like our popular 2,5 L HDPE bottle, the smaller version has an ergonomically perfected design to ensure a firm grip and full control – no matter how big or small your hands
- Developed with scientists, for scientists. Today's performance requirements for lab reagents go well beyond product properties. Besides analytical purity, aspects such as handling, safety, ecology and economy play an increasingly crucial role for our customers
- All of these factors are directly influenced by packaging – particularly for acids, bases and solvents. Glass bottles are still the preferred option. As a container for all types of chemicals, glass is a valuable inert material for daily lab use. But there is always the risk of breakage
- At Merck, we have been developing the most innovative and practical packaging concepts for many years. Our experts have collaborated with scientists like you to come up with the perfect packaging for solvents, acids and bases: Our HDPE (high density polyethylene) bottle range. Developed and used exclusively by Merck, it incorporates safety, environmental protection, and cost savings along the entire process chain. Meet our new 'easy grip' bottle and feel how it makes your lab work safer, quicker and easier every time

FIND OUR PRODUCTS HERE : 

Extran® Protects Your Work, Your Personnel and the Environment

For over 30 years, Merck's Extran® cleaning agents have enabled proper scientific working procedures in laboratories and production facilities all over the world. Thanks to their thorough, residue-free cleaning, Extran® products ensure that everything that comes into contact with chemicals or biological substances is free of impurities – both before and after use.

Despite their exceptional cleaning strength, Extran® products use biodegradable ingredients that are free of toxins, so they are especially gentle on the environment and on the health of laboratory staff.

FEATURES AND BENEFITS

- Reliable, residue-free cleaning
- Free from scents, dyestuffs, chlorine and other toxic ingredients
- All active ingredients are biodegradable
- The ideal all-purpose cleaner
- Validation support to prove the absence of surfactants after the cleaning process

FREE OF RESIDUES, TOXINS AND WORRIES

Extran® cleans reliably, leaving no residues. Hence, it prevents contaminants from being transferred into your next analysis or test. For added certainty, Merck provides a practical and easy-to-use application aid to prove the absence of non ionic surfactant residues by means of a photometric test. This helps you prepare your own cleaning validation, thus saving you time and costs.

Extran® not only supports your work, but also protects the health of laboratory staff. Our cleaning agents contain no chloride or other toxic ingredients and avoid all scents and dyestuffs. Extran® products are also free of silicones and oxidants, and have no inhibitory effect on enzyme tests, such as NTA, α-amylase, LDH, GOT or on acid phosphatase. So, for safe, secure laboratory cleaning, there's no better choice than Extran®.

THE 'GREEN' WAY TO CLEAN

At Merck, we believe that cleaning laboratory utensils shouldn't mean polluting the planet. That's why Extran® cleaning agents are produced from biodegradable active ingredients under strictly controlled conditions, and fulfil the highest standards in environmental protection. What's more, Extran® almost completely eliminates the need for the toxic cleaning agent chromo sulphuric acid, which is still commonly known on the market but already prohibited for cleaning glass vessels. This makes our Extran® cleansers both user-friendly and eco-friendly.

ALL-PURPOSE SOLUTIONS FOR AUTOMATED OR MANUAL CLEANING

Merck's Extran® products are true all-purpose cleansers. Depending on the type of contamination and the material to be cleaned, Extran® cleaning agents offer the ideal solution for the cleaning of your laboratory utensils and production facilities. The range includes detergents for manual cleaning or automated cleaning in laboratory washing machines.

Reliable Drying Agents for All Your Applications

Drying agents (desiccants) from Merck are the ideal choice for your drying applications in the lab or in production and as well as for storage and transport. Our user-friendly products are suitable for a wide range of applications – from the drying of gases, liquids or solids using static or dynamic drying processes to the protection of goods and materials from moisture, mould or corrosion.

Merck's high quality drying agents include calcium chloride, silica gel, molecular sieves, desiccant sachets, and many more. A broad selection of products with different properties with respect to e.g. water uptake rate, absorption capacity, particle size, or regeneration possibilities ensures that you will find the suitable desiccant for your specific application.

In addition to our high quality drying agents for laboratory applications, we provide a comprehensive range of products specially designed to minimise the effect of moisture on your products. Thanks to their high reliability, efficiency and ease of use, Merck desiccants help you to protect your valuable goods, reduce costs and increase the longevity of your products.

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Emergency help

There is a lot you can do to prevent safety risks. But, especially when working with glass bottles or open vessels in labs, accidents can happen anytime. To avoid serious injuries, it is important to act quickly but wisely. With the Chemizorb® range, we offer a one-stop solution for rapid, reliable absorption and neutralisation of unpleasant liquid spills.

Chemizorb® Absorbents – Easy Cleaning of Spilled Liquids

Accidental spills of hazardous liquids can happen in any lab. With Chemizorb® from Merck, you can remove harmful, aggressive or other unpleasant liquids quickly, safely, and eco-friendly.

Chemizorb® absorbents consist of porous mineral or synthetic copolymers that are chemically inert and capable of taking up huge amounts of liquid – 100 to 400% of their own weight, depending on the material. The Merck Chemizorb® product range includes 'all-rounders' as well as specific absorbents for different substances.

Our all rounder absorbents Chemizorb® powder and Chemizorb® granules are characterised by a high absorbance capacity for aqueous solutions (acid, alkalis), organic solvents and viscous oils. While granules possess a lower absorbance capacity than the powder, they are much easier to dose and can be used in places where powder proves unsuitable, e.g. in draughty rooms or outdoors.

Our 'specialists' for alkalis (Chemizorb® OH-), for acids (Chemizorb® H+) and for hydrofluoric acid (Chemizorb® HF) additionally contain water-soluble neutralisers as well as pH indicators to keep track of the neutralisation process. Aggressive acids and alkalis can thus be removed more efficiently and safely.

Last but not least: the 'all in one' mercury set. Chemizorb® Hg includes all reagents and auxiliaries you need to safely and completely remove drops and traces of mercury. The reagents included in the set are sufficient for the safe decontamination of an approximately 1 square metre area.

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